THE "NEURILITY" OF THE KIDNEY

A MONOGRAPH ON NERVE SUPPLY TO THE KIDNEY

by

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BLACKWELL
SCIENTIFIC PUBLICATIONS
OXFORD

Published simultaneously in the United States by
Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Illinois

Published simultaneously in Canada by
The Ryerson Press, Queen Street West, Toronto, 2

First published March, 1952

Printed in Holland for BLACKWELL SCIENTIFIC PUBLICATIONS by
VERENIGDE DRUKKERIJEN HOITSEMA N V GRONINGEN

TO MY WIFE

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FOREWORD

The application of modern methods of investigation to the study of renal function in normal and pathological conditions has elucidated a number of problems which were not well understood a few years ago, in particular the development of biochemical techniques has helped to advance the interpretation of kidney function in a way which would otherwise be lacking With the clearance methods the three assumed stages of urine formation, i e filtration reabsorption and secretion, have been carefully analysed although there is still an ample field open to speculation From these biochemical studies and from other fields of approach one thing appears to be certain, namely that the kidney has an almost unique capacity to adapt itself to the requirements of the body as a whole an exquisite adaptability which cannot be readily understood without accepting an equally rich innervation of this organ

The sensitivity of the kidney to nervous stimulation was an early finding of Claude Bernard which Vulpian confirmed and which has repeatedly been demonstrated But the finding that the denervated kidney also shows a certain capacity for adaptation even if more limited or altered from the normal, seems to indicate that the kidney possesses an autonomous innervation which can control kidney function independently from the higher centres A large number of accurately observed facts indicate that the unique and characteristic behaviour of the kidney depends upon its nervous and vascular components Some illustrative examples of this are

1 In monkeys and cats it has been found that during pressor responses evoked by electrical stimulation of some parts of the cerebral cortex the limb volume usually increased while the kidney volume diminished The intra arterial injection of Indian ink during such experiments shows the virtual exclusion of the ink from the vascular bed of the renal cortex
2 Haemorrhage in frogs and rabbits and asphyxia in frogs causes a marked constriction of renal cortical vessels but if a splanchnicectomy is previously performed such a constricting effect is always markedly decreased when not totally prevented
3 Intra arterial injection of a low concentration of phenol urethane which does not cause vasoconstriction in the legs does *constrict the renal arteries*
4 Bilateral renal cortical necrosis in human pathology is a measure of the damage that may follow alterations of blood flow within the kidneys This alteration is probably due to a spasm of the cortical arterioles

Even the interpretation of findings of the clearance method needs to assume an independent and exquisitely fine response of small segments of the intrarenal arterial tree such as the afferent and efferent arterioles of the glomerulus

It is a fact that the profuse literature on the investigation of renal function

by "clearance" methods has not been paralleled by comparable work on the detailed neuro-vascular architecture of the kidney, and in this sense this book by Dr De Muylder is a welcome contribution to the understanding of such minute intrarenal arrangements His personal work, both in America and in Belgium, has permitted him to incorporate into his methods that which he has found beneficial in both these schools As a Belgian it is not only natural but indeed satisfactory, that he brings into his monograph a wealth of information from the school to which he belongs, and in several instances his personal contributions *serve to integrate previous work by some of his* colleagues More than this, he brings forward data which, up to now, have not been sufficiently appreciated For instance, that neither the nerves of the *metanephric blastema nor those of the* ureteral bud innervate the medulla propria and he insists that the nephron must be considered as a neuro-vasculo-tubular unit He dismisses the existance of secretory nerves, pays due attention to the innervation of the intrarenal veins and suspects that the area between cortex and medulla (the juxta-medullary region) has a sensory nerve supply and that nerve endings may be found in the veins of the kidney, resembling the presso-receptors of the large veins of the cardio-pulmonary area

On several points De Muylder's work is a challenge to accepted traditional views, but when findings give way to speculation this is not brought forward to claim new knowledge but to fill existing gaps until new data removes or confirms what he has tentatively put forward

Having been personally engaged in an investigation of the role of the nervous and vascular systems in the conditioning of kidney function I am acquainted with the enormous difficulties of integrating data from fields so widely apart *as those of biochemistry, radiology, histology, physiology,* pathology and clinical medicine Four years ago, with some colleagues, I published the findings of the different behaviour and, not infrequently, opposite response of many *of the renal cortical vessels to those of the renal medulla, a finding which* has been repeatedly observed in our experiments with rabbits and which has also been confirmed by a substantial number of other investigators working both with rabbits and with other species, including *monkeys Some workers,* however, claim they have been unable to confirm our observations and the facts are still under scrutiny *If such an observation, which has been readily* repeated and can be visually recorded, has not been confirmed by other research workers, it is not surprising that the integration of so much more complex and frequently conflicting data takes such a long time and sustained effort Dr De Muylder's contribution will help to increase our knowledge and to focus the attention of many observers on the role of the nervous system in controlling the blood flow through the different components of the nephron

J Trueta

PREFACE

ABOUT fourteen years ago, when we began a study of the nerve supply to the idney, we did not fully realize the manifold possibilities of the subject, its in imate relationship to some pathological problems became obvious to us only

We decided therefore to review available published data and to initiate a new examination of the anatomy of the renal nerves We soon became aware hat the argument mainly revolved about the microscopic anatomy of the in rarenal nerves, and we have concentrated on this subject Our line of approach to this problem may be summarized as follows first, we decided to use a tech nique for staining the visceral nervous system which would not be vulnerable to basic criticism at the present state of our knowledge, second, because the nerves in the adult kidney form very intricate plexuses, we chose to study them during development from early embryonic to adult stages, so that we could witness the constitution of the more elaborate picture displayed by the adult This policy proved to be a very gratifying one in various respects, the results of nervestaining are much more successful during early stages of life and we have been able to describe structures which have not previously been described

During the course of these investigations, our attention was drawn to the juxtaglomerular apparatus The significance of some of the components of this apparatus became clear as we came to understand how they reacted under nephrosclerotic conditions and how they might be linked to a special type of neoplastic degeneration Comparative anatomy enabled us to understand various facts which would otherwise have remained obscure Comprehensively, our knowledge of the innervation of the kidney appears to fit very closely the more recent advances in renal physiology and experimental pathology We are acutely conscious of the fact that many important problems remain unsolved, but it seemed advisable to summarize our present data and to make a general survey of the subject available to those who are interested in the role of the nervous system in the functioning of the kidney

ACKNOWLEDGEMENTS

We wish to express our gratitude to those who helped us in the preparation of this monograph to Professor E van Campenhout without whose advice and criticism this work would never have been done, to Professor P Lacroix for his encouragement and for many photomicrographs, to Professor D H Barron who enabled us to study a series of sheep embryos, while being at the University of Cambridge to the department of Gynecology and Obstetrics of the University of Louvain (Prof R & J A Schockaert) for kindly allowing us to use some of their embryonic material to the department of Surgery of the University of Louvain (Prof G Debaisieux) for the opportunity to study surgical specimens, to Mr G Wijns of the University of Brussels for the photomicrographs, to Mrs Gerebtzoff, Miss Piotti and Mr Brullemans who made our drawings and diagrams, to Dr R E Livingston for reviewing part of the manuscript, to Professor P Gerard and Professor A Policard for their permission to reproduce illustrations already published in the 'Archives de Biologie' and in the 'Bulletin d Histologie appliquee' respectively, to all those who helped us to carry on our work, were it but by not interfering with it

Ch de Muylder

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CHAPTER I

Normal innervation of the kidney

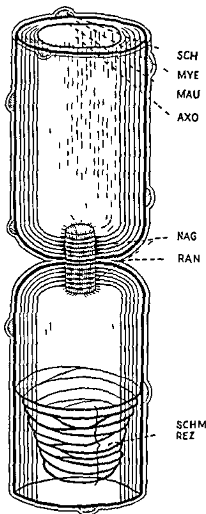
A TECHNICAL REMARKS

THE microscopical innervation of the kidney in various species of mammals (mouse, rat, guinea pig, cat, dog, etc including man) appears to be remarkably constant, when examined by the same method, CAJAL's reduced silver technique, the specificity of which is well-known

Recently, though, there has been some argument about the type of nerve fibers actually stained NONIDEZ (1939, [144]), NONIDEZ & HARE (1942, [146]) and WRETE (1950, [207]) have claimed that the orthosympathetic postganglionic fibers remain unstained or take a light-brown colour RANSON and BILLINGSLEY (1918, [61]) had already expressed similar views WEBER (1940, [205]), BAUMANN (1941, [8]), ELFTMAN (1943, [6]), UNGEWITTER (1943, [189]), HARMAN and DAVIES (1948, [92 93]) have noticed significant differences between deep- and light-staining fibers, the deep-staining ones generally being of the vagal' type and the light-staining ones of the "sympathetic" type It is difficult, however, to make a didactic statement because of the rather common observation of varying darkness of the black colour from the periphery to the center of the specimen submitted to silver impregnation a nerve fiber may show different shades along its course through the tissues We agree that some fibers are darker than their neighbours, but we prefer to differentiate fibers by their structure, thickness and the degree of myelinization Altogether, the various morphological characteristics, among which the quality of impregnation is the most obvious but not the most important, may have a special meaning (ortho or parasympathetic fibers, pre- or post-ganglionic or cerebrospinal fibers) and the observer is on more solid ground if he takes all of the characteristics of the fiber into account rather than rely upon the shade of brown or black to determine his classification

The real nature of the morphological characteristics of the nerve fibers is not known NAGEOTTE (1922, [39]) has published a reconstruction of a myelinated nerve fiber, which is classical, not unfrequently nerve fibers are seen showing various structures appearing in NAGEOTTE's general picture The appearance of the sheath of myelin itself varies considerably the same is true

of the nerve fiber, the axoplasma, the neurofibrils, and the so called MAUTHNER's sheath We do not know to what extent the various aspects correspond to the structure of the living stage Various works, by J Z YOUNG (1936,[208, 209] 1937,[210]) mainly, using giant axons from Cephalopods, Crustacea and Annelids threw some light on that problem It may be suggested for the time being that if neurofibrils do not exist in the axoplasm, at least there is some inner longitudinal organization of the molecules, there must be an interphase between the semi-fluid axoplasma and the sheath of myelin, the fatty layer is sandwiched between the fiber proper and the SCHWANN cells, unmyelinated fibers seem to have a fatty layer obscured by the presence of proteins, a fatty layer may sometimes be present outside a fibrocytic layer, and so on Other aspects are accounted for by a variety of pathological and experimental phenomena For the purposes of this study we need not be concerned with all of the discrepancies between the nerves in vivo and on stained sections We require only a technique without too many artefacts, and producing them consistenly Our experience confirms that CAJAL's reduced silver impregnation fits these requirements This technique might not show all the finest nerve fibers but the fibers shown by the properly applied method are beyond any doubt nervous structures As mentioned above, there is more than one test for establishing the nervous nature of a fiber or a cell, among these "marks" of "neurility" are the shape or contour, the internal structure, the affinity for various stains and the lack of affinity for others Bearing this in mind at every stage of the researches, one should not label "nervous" every black or brown fiber encountered in a section – even if the tissue is supposed to be correctly impregnated by either one of the classical, or the modern, fashionable, silver-stains – without



SCHM SCHMIDT LANTERMANN incisure REZ network of REZZONICO inside funnel of GOLGI The outer layers represented by the PLENK LAIDLAW sheath, the mesh work of KEY and RETZIUS and epineurium are not pictured in this reconstruction The network of neurokeratin is omitted too although it is sometimes very useful to ascertain the presence of myelin

first establishing the presence of typical SCHWANN-cells or their cytoplasmic syncytium, of myelin sheaths, of eventual MAUTHNER's sheaths, of axoplasma, axons and neurofibrils

We controlled our results by various other techniques, such as the ROGERS method (modification of BIELSCHOWSKY's silver-impregnation, for paraffine sections) [1], MASSON's trichrome (iron hematoxylin, ponceau of xylidin and acid



FIG 2 Human semi lunar ganglion after reduced silver impregnation this technique was used for the majority of our specimens and fits the requirements referred to in the text

fuchsin, anilin blue or light green) silver impregnation of reticulin (FOOT), haemalun eosin, a s o

As the results of these different methods complemented each other, we were able to obtain an overall picture which we believe to be quite complete and comprehensive

Great care should also be exercised in correlating structure and function K KURE, for instance, (1933, [20]) concluded from his observations on the splanchnic nerves that the fibers with a visible myelin sheath and which were thicker than five micra were of a gustative type (because they were never

[1] We are indebted for these controls to prof E VAN CAMPENHOUT who applied ROGERS method to some of our material

found in the splanchnic area and because such a sensivity was absent in the same area) and that the fibers which had a caliber of three to five micra conveyed the sensations of pain. Having demonstrated both types of fibers in the renal area, KUBO (1935, [119]) denied KURE's hypothesis, because there are no gustative impulses arising from the renal area, and no painful stimuli arising from the renal parenchyme (where the smaller fibers were seen).



FIG 3 Photomicrograph of a ganglion in the hilum of the kidney of a human newborn such ganglions are very frequent in this location MASSON's trichrome

Because the main difficulty to the examination of renal nerves has always been the propre staining of nervous structures, we felt that technical discussions which might be helpful should be included. This view will be supported by a short summary of the published data

B *Position of the problem*

Many communications have been devoted to the study of renal innervation. The majority of these are referred to in our previous publications and we mention here only the most important historical features We give first a brief list of early textbooks where reference to renal innervation may be

found[1], but, as gross dissection of the renal hilum reveals the presence of many nerves and ganglions, we shall not make any particular mention of such descriptions, nor shall we discuss the significance of their variations

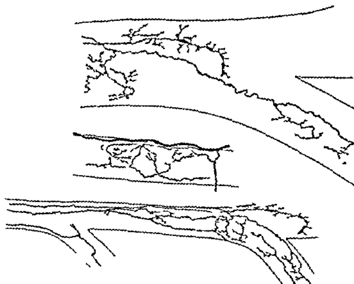


FIG 4 Drawing of arterial nerve endings in the kidney according to VAN GEHUCHTEN Silver impregnation (GOLGI)

KOLLIKER V, Handbuch der Gewebelehre des Menschen, 1863—1867
Periarterial nerves are followed to interlobular arteries, no endings are demonstrated

LUDWIG, C, in STRICKER's Handbuch der Lehre von den Geweben des Menschen und der Thiere
Periarterial plexuses with a few ganglions exist, but their endings are unknown

FREY H Handbuch der Histologie und Histochemie des Menschen 1874
The structure and function of intrarenal nerves are unknown

KRAUSE W Allgemeine und microscopische Anatomie, 1876
The renal nerves are probably exclusively vascular

TOLDT K Lehrbuch der Gewebelehre, 1877—1888
There are perivascular renal nerves but their endings are unknown

SCHAFER in QUAIN's Elements of Anatomy vol 2, 1882
Renal nerves are small arise directly from the renal plexus and the small sympathetic nerve and contain fibers originating as well from the sympathetic as from the cerebrospinal system They are followed up along the fine arteries but their endings are still not known

VAN GEHUCHTEN A, Anatomie du système nerveux de l'homme 1892
See fig 4 and summary table below

[1] This list is not exhaustive the descriptions are quoted mostly from RETZIUS (1892 164) more references to early textbooks are mentioned in D EVANT's contribution to this subject (1899 45)

TABLE 1

Name and Year	Material	Methods	Observations: 1 Vessels and connective tissue	Observations: 2 Nephron itself
PAPPENHEIM 1841	3 year old child 30 year old man		Nerves follow intrarenal arteries, they are demonstrated along arteries of $^1/_8$ in diameter (0 3 mm) No ganglionic cells	
HOLBROOK 1883	Pig, sheep ox, cat, man (child)	COHNHEIM LOWITT (chloride of gold)	Many nerves, mainly non medullated in periarterial layers and bundles, they form the plexuses of the afferent vessels and reach the capillaries of the tuft, with nerve fibrils in the walls and between the smooth muscle cells Small number of true ganglia	Non medullated periarterial nerves give off peritubular plexuses on either side of membrana propria, with delicate fibrils in the cement between epithelial cells, inosculating with intercellular spokes Exceedingly scanty non medullated nerves, apparently independent from arteries, in the pyramidal substance
RETZIUS 1892	Young mouse and rabbit (11 days)	GOLGI	Periarterial plexuses with knob like endings on smooth muscle cells, reaching vasa afferentia, ending where glomerulus begins (free endings around arteries and in vascular hilum of glomerulus) No ganglionic cells	No tubular nerves
VAN GEHUCHTEN 1892 1897	Mouse and rat	GOLGI	Free ending twigs in walls of blood-vessels (See fig 4)	
BERKLEY 1893	(Dog), mouse	GOLGI (modified)	Periarterial non medullated plexuses (some fibers are extremely fine, some are quite coarse and broad), giving off short branches with end bulbs on smooth muscle cells, extending to BOWMAN's capsule in a meshwork surrounding the capsule without entering it and bearing round knob like endings No nerves connected with venous trunks nor on vasa recta Numerous ganglionic enlargements of the fibrils but no real nerve cells(?)	Arterial plexus gives off fibers to tubuli contorti wrapped in fibrils supplied with endings on and inside membrana propria Also fibers around and between collecting tubulus In purely medullary areas nerve fibers are very rarely met with

KOLLIKER 1893	Mouse (24 d old)	GOLGI (fast)	Rich plexuses along arteries up to MALPIGHI's corpuscle with endings upon corpuscle and fibers running around *it to opposite pole to form a* meshwork on efferent vessel and send branches between tubules branches also reach renal capsule where they show endings	No nerves on tubules themselves nor in the medullary proper
AZOULAY 1894	Man human foetus	GOLGI	Plexus of non medullated varicose fibers unfrequently around vessels No definite nervous cells No interstitial nervous cells	Plexus mostly penetrating through medullary renal substance where a few fibers stay while others reach the cortex which exhibits many free narrow fibers with knob like endings on the wall of tubular cells or glomerular epithelium (probably not yet true endings)
AZOULAY 1895	2 day old guinea pig	CAJAL (fast)	Strictly periarterial nerves with knob like endings turning around glomeruli to renal lobules giving off 1 or 2 *small branches to the vas afferens* entering the glomerulus where they give 2 to 4 varicose branches to the inner aspect of BOWMAN's capsule and between the capillary loops sensory branches regulating blood pressure through vasomotor nerves	No tubular nerves
PENSA 1891	Rabbit guinea pig mouse	GOLGI	Very rich periarterial plexuses with endings on smooth muscle cells and varicosities forming a plexus around BOWMAN's capsule or more often sending fibers running around the capsule and ending afterwards endings on the capsule itself and very scarce fibers entering the tuft to end on capsular epithelium and capillary loops Ganglionic cells (?) and pseudo ganglionic cells belonging to connective stroma(?)	Arterial plexus gives off varicose fibers to tubules following membrana propria ending on it or between epithelial cells

Name and Year	Material	Methods	Observations: 1 Vessels and connective tissue	Observations: 2 Nephron itself
D'EVANT 1899	*Man* (foetus, child, adult) *Mammals* Rabbit Guinea pig, mouse, rat, dog, cat, dor mouse, newborn puppy *Reptiles*, *Amphibians*, *Fishes*	GOLGI CAJAL LOWIT-RANVIER, APATHY, EHRLICH, PALADINO	Rich periarterial plexuses with knob-like endings, and others, on the vascular wall, and endings on glomerules Free nerve endings between tubules Nervous cells in parenchyme without pericellular capsule	Periarterial plexus sends fibers ending on the wall of the tubules
v SMIRNOW 1901	*Embryos and newborn* man, dog, cat, rabbit, mouse, white rat, guinea-pig *Adults* man, dog, cat, mouse, guinea-pig, squirrel, hamster, bat, tamia (*Metanephros*) *Fish, amphibians, reptiles* and *birds*, incomplete results (*pro- and mesonephros*)	GOLGI EHRLICH		Endings on tubules, on membrana propria and between epithelial cells all along the nephron
DISSE 1898—1902	Adult mouse	GOLGI	Usual periarterial plexuses	Arterial plexus gives off branches to tubules to form sketchy peritubular plexuses (tubuli contorti) with endings on membrana propria, and on BOWMAN's capsule No medullary nerves
RENNER 1913 1920 (1931)		(BIELSCHOWSKY, EHRLICH)	Perivascular plexuses to vasa afferentia and efferentia with motor muscle endings Non medullated fibers and scarse medullated ones No intrarenal ganglionic cell	
CHABADASCH 1927	*Rana esculenta* *Rana temporaria*		Same results as SPANNER	

CHABADASCH 1927	Rana esculenta Rana temporaria Bufo vulgaris		Same results as SPANNER	
SPANNER 1928	Rana agilis and mostly Anguis fra g lis	Methylene-blue	Perivascular plexus mainly periarterial forming a pericapsular (BOWMAN) net and extending to tubules Ganglia present	Periureteral plexus extending to practically all tubular segments but mainly to excretory system Tubular nerves from arterial origin
AKIMOTO 1928	Frog toad turtle pigeon cock duck mouse rat, guinea pig rabbit dog man P geon n avita minos s B	CAJAL (modified)	Periarterial nerves and plexuses (medullated and non medullated) with end bulbs in the vascular wall and many terminal branches on BOWMAN's capsule and fibers inside glomerular tuft Vascular nerves are clearer than tubular nerves Oedema and atrophy of nerves in disease	Vascular nerves send tubular nerves to form peritubular plexus branching with knob like endings outside the basal membrane and inside, in the basal part of the epithelial cells
HIRT 1930	Frog	Methylene-blue (with critical remarks)	Nervous vascular net giving intraglomerular nerves through hilum and capsule without true visible endformation Non medullated nerves	Tubular nervous net
KAUFMANN and GOTTLIEB 1931	Rat guinea pig cat dog man	BIELSCHOWSKY (modified) EHRLICH (with technical remarks)	Non medullated periarterial plexuses in adventitia and media of arteries plexuses on veins too nerve endings in arterial wall and in glomeruli along the capillaries	From periarterial plexuses are build up peritubular plexuses, in cortical as in medullary areas, on membrana propria with fine varicose branches and endings on membrana propria and between epithelial cells
DAMBRIN 1932			No original microscopical researches	id
KUBO 1933	Man dog rabbit horse rat pigeon chicken toad frog	CAJAL (modified)	Periarterial plexus extending to precapillary vessel with endings inside vascular wall and inside glomerulus Majority of non medullated fibers except in birds where the medullated ones are the majority Normal ganglionic cells mostly in hilum Microganglionic cells(?)	Arising from periarterial plexus exists a peritubular plexus outside membrana propria with various endings (bulbs twigs) even between epithelial cells

TABLE 1 (*Continued*)

Name and Year	Material	Methods	Observations: 1 Vessels and connective tissue	Observations: 2 Nephron itself
KANDA 1933			Spinal parasympathetic innervation	
KUBO and CHOJA 1933	*Pigeon*, dog, rabbit	CAJAL (modified) Experimental study	Medullated and *non medullated* periarterial, and periureteral nerves to pelvis and calyces Small *number* of fibers inside BOWMAN'S capsule Coeliac plexus resected *in dog* after 24h, nerve hypertrophy, after 72h, nerve degeneration	Peritubular plexuses with endings on membrana propria (?) No intracellular endings, no secretory nerves
NAGAI 1935		Injection of contrast substances into nerves		
KUBO 1935		I Experimental study of nerve-poisoning II Unilateral cervical vagectomy, *uni- or* bilateral abdominal splanchnectomy III Excision of *coeliac plexus*, with coeliac gan*glion*	I Various degrees of swelling, *atrophy* and disappearance II Nerves intact III Degeneration of nerves In renal hilum, thick medullated fibers larger than 6 micra In renal parenchyme, thin medullated fibers, between 3 and 5 micra	
MONTICONE 1940			No original microscopical *researches*	
DE MUYLDER			See text	

OBERLING 1944	Man	GROS SCHULTZE	Rich plexus along vas afferens (part of it coming from the nearby parenchyme) with endings on cells of vascular wall (Possibility of presence of medullated fibers) Thin fibers entering glomerulus and fibers to outer layer of BOWMAN's capsule Bulk of fibers turning around glomerulus to end in near by parenchyme (by pass)	No data on secretory nerves
EPSTEIN and SOTELO 1946	Man (human foetus)	Reduced silver impregnation	Periarterial plexuses Thin and thick fibers (receptor vasodilator and vasoconstrictor) Free interstitial nerve endings in connective tissue arising from thick fibers giving off thin branches (some of them for vascular channels)	
HARMAN and DAVIES 1948	Cat rat	BODIAN	Periarterial nerves forming a complex of nerve fibers pervading the perivascular space of the glomerulus endings in perivascular tissue of *glomerular tuft*	Nerve endings in epithelium of convoluted tubule (T C I)
d 1948	Mouse rat cat macaca		Coiled vessels between arteries and veins with epitheloid modifications in renal sinus richly supplied with nerves Many medullated nerves	
KNOCHE H 1950	Man (foetus and adult)	BIELSCHOWSKY GROS (thick frozen sections)	Terminal reticulum in outer layers of vessels and outside BOWMAN's capsule as well as on glomerular tuft	Perivascular nerves give off non medullated branches forming a terminal reticulum on the convoluted tubules

The other references are given in Table I This table shows that nearly every possibility has been described as a fact and that *nerves have been* demonstrated at one time or another in every single part of the kidney Such a table demonstrates the widespread discrepancy among the various results and *emphasizes the* need for renewed investigation with a reliable histological technique

The principal unsolved problems, for the time being, may be stated as follows

1 Are there intra epithelial nerve endings in the nephron, to which a *secretory function might* be ascribed?
2 Is there any special nervous device regulating the blood flow through the glomerulus, and, secondarily the blood supply to the tubules?
3 Is there any evidence of a connexion between the renal nerves and the source of hypertensive mechanism?

These problems are closely related to various forms of pathology, including nephritis or nephrosis, nephrosclerosis, high blood pressure, crush-syndrome, eclampsia, and even neoplasms

C Microscopical data

The embryology *of the third, permanent renal organ of the higher vertebrates* (metanephros) is well known, it develops from two "anlagen" a metanephrogenic blastema and an ureteral bud

The ureteral bud arises from the pelvic portion of the wolffian duct and grows cephalad towards the lateral lumbar mesenchyme where the metanephrogenic *blastema develops The blastema appears as a condensation* of lumbar mesenchyme which the branching of the ureteral bud splits into small cellular masses, the spheric isolated masses assume early the shape of an inverted capital S while a lumen appears in their central part, they form thus a tubular sketch The half of the S directed towards the hilum forms Bowman's capsule, *while the* peripheral half differentiates into the tubule itself, including the "pars intermedia" at the junction with the ureteral bud, the latter forms the "tubuli recti" and the excretory system proper These two "anlagen" have their individual blood supply *Our studies show that they have also their individual nerve supply*

The nerves reach the kidney (metanephros) between the 38th and 43rd day (30 to 55 mm) in the sheep embryo, and before the 9 mm stage in the mouse embryo (personnal observations) According to Pirner (1949, [160]) fibers reach the kidney on the 5th day *of incubation in the chicken embryo*, on the 6th day of incubation, Van Campenhout (1931, [91]) saw the renal plexuses around the origin of renal arteries, but no intrarenal fibers

The nerves pervade the kidney along two different pathways They follow the blood vessels of the hilum, mainly the renal artery, or the ureter and





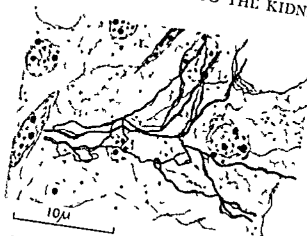


FIG 7 High magnification of drawing of the nervous plexus applied on the wall of the uretero-pelvic junction of a newborn mouse Reduced silver impregnation

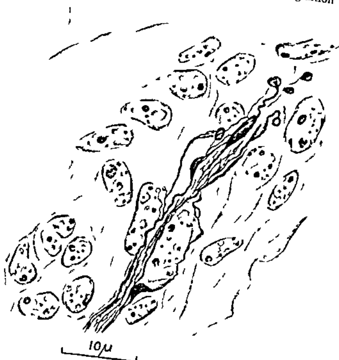


FIG 8 Bunch of nerve endings in the outer layer of an intrarenal arteriole, in a 10 mm mouse embryo this drawing shows very clearly the syncytial disposition of the fibers Reduced silver impregnation

eventually its blood vessels. In both cases, they finally arise from the plexus surrounding the aorta and the iliac arteries and the ganglia spread along these vessels; sometimes fibers arise directly from the ganglia of the lumbar sympathetic chain. This set up becomes obscured as the embryo grows. We never demonstrated nerve fibers entering the kidney through the capsule or



Fig. 9. Periarterial nerve plexus in a mouse embryo; the artery runs between two lobes; its wall is build of flat endothelial cells, epithelioid muscle cells and a few fibroblasts surrounding the nerve fibers. 14 mm mouse embryo. NONIDEZ reduced silver impregnation.

the convexity of the organ. If such fibers exist, they are probably unimportant under normal conditions.

Entering the kidney through the hilum with the vessels and with the ureter, the nerves form plexuses in which it becomes difficult to recognize the fibers belonging to either group. This question, though, may be answered to a certain extent by embryological studies. At the stages where it remains possible to follow the ureteral nerves as such, they do not extend any further than the insertion of the calyces on the papillae, while the vascular nerves branch all through the renal parenchyme along the vessels up to the outer limit of the cortex.

The "ureteral nerves" should be distinguished from the fibers supplying the ureteral vessels, although they have the same origin both arise from the plexus and ganglia surrounding the iliac arteries, where these are crossed over by the ureters, branches also come off other ganglions lying deeply on both sides of the rectum, the uterus and the bladder The "ureteral nerves" form a loose

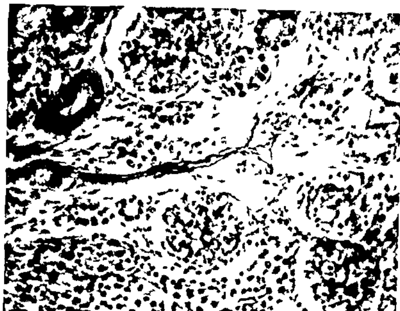


Fig 10 The nerves of the interlobular artery of a 20 cm human foetus with the finest twigs extending along the preglomerular arteriole Reduced silver impregnation

network in the outer layer of connective tissue surrounding the ureter, they reach downwards the outer layer of the bladder and upwards the renal pelvis From this plexus small branches and isolated fibers enter the muscle coat of the duct where they form very simple knob- or ring-like endings between or upon the smooth muscle cells, we never saw them entering the mucosa On their way towards the pelvis, and mainly in the vicinity of the uretero pelvic junction they may come in close contact with cells which in the early stages resemble sympathoblasts, at later stages small islets of ganglionic cells may be found there although infrequently We saw, for instance, a typical micro ganglion in the outer layer of the pelvis of a young mouse, where the main nervous network is located, this network branches off and sends tiny fibers to form a much looser plexus closely applied to the muscle coat, with knob- or ring-like endings between the muscle cells or upon them

In the renal parenchyme, the "vascular nerves" follow mainly the branches

of the arteries, and the veins to a lesser extent Here again, the bulk of the nerve supply is to be found in the adventitia, it forms a well developed plexus from which smaller branches arise, entering eventually the media where they end always in the same fashion fan-like, knob-like, club or ring-like terminal en-

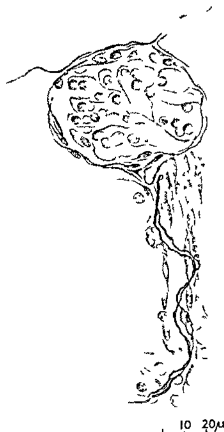


FIG 11 The nerves on the afferent arteriole different levels are drawn on the same picture Adult mouse reduced silver impregnation

largements upon the muscle cells Not a single fiber was ever seen coming in close contact to the intima

In connexion with the periarterial plexus one may find intrarenal "micro-ganglia" We found them in young mice where they may be rather frequent in some individuals, and lack completely in others We found but one ganglionic cell in the renal cortex of an adult mouse, along a small artery In one case, in

a young mouse, one of the little nests of nervous cells was accompanied by a few epithelioid cells, surro . tiny paragan-glionic body. Ganglionic sometimes in large numbers in birds a red to in due course. The existence of intrarenal nervous cells is thus a fact; its importance,



FIG 12 Nerve cell in the outer layer of an intrarenal arteriole. Newborn mouse RANSON's silver impregnation Drawing oc 16, obj 100 imm.

of course, is open to discussion. As several authors reported their existence and other ones denied it, it may be of interest to point out that reviewing the literature on intrarenal nervous cells, and on innervation of the kidney as a whole, is a particularly trying experience and that care should be taken to find out what the authors report as actually seen by themselves or what they quote from other works; it is also of utmost importance to have a precise idea of the material studied, the extent of the study and the technique used. We expressed our views on the technique previously. It should be borne in mind that the existence of one particular structure found only once, figured in an original paper and quoted or reproduced afterwards by the majority of the authors may outweight some other extensive and unsuccessful researchwork of

long duration, and thus give the false impression that such a structure is frequent simply because it is oftentimes quoted We thus underline the assertion that after an extensive search through the sections of several hundreds of kidneys in various mammals, we only found intraparenchymatous nervous cells in the conditions described above Some results raise the question as to whether



Fig 13 Intrarenal microganglion at the bifurcation of an interlobar artery Newborn mouse reduced silver impregnation Drawing oc 16 obj 100 imm

the *characterization of a nervous cell in the kidney should be the same as* anywhere else in the body To illustrate this point, we cannot do better than quoting first, one of the earlier works on the subject ' ganglionic enlargements, sometimes of considerable extent, occur among the fibers adjacent to the blood vessels, or even separate from them, and on the whole, local enlargement of nerves throughout the kidney is not infrequent Varicosities of the smaller fibers occur everywhere Owing to the intensely black staining no cell structure is visible in these local ganglia, nor can nerve cells, strictly speaking,



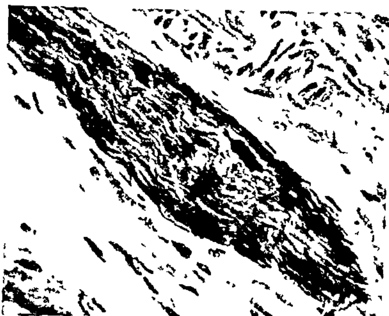


Fig 14A and B In the kidney of a dog, a nerve fiber enlargement among normal looking fibers, may be followed on a few serial sections without showing any nucleus ?pseudo-nerve cell (Low and high magnification) Roger's silver impregnation on slide

be made out within the limits of the kidney". (BERKLEY, 1893, 17, p. 410). W might also mention KUBO's (1933, 117) description of ganglionic cells in th renal system including a normal form which is found mostly in the hilum of the kidney, and microganglionic cells found in the pelvis and the calyces of all



FIG 15 The nerves of the vascular pole of the glomerulus run on the base of the macula densa between the glomerulus and a slightly oblique section of T C II Adult mouse reduced silver impregnation Drawing oc 16 obj 100 mm

animals, and in the medullary of the dog, KUBO states: "Über das Vorhandensein dieser Mikroganglienzellen wurde von jeher viel diskutiert, besonders sind es die Ganglienzellen in dem Mark die bisher von niemandem beobachtet wurden"

We believe that similar criteria should be applied to cell bodies as to nerve

fibers one should recognize as nervous cells only these which exhibit well established marks of "neurility" Let us repeat that such cells are found scarcely and irregularly, in the vicinity of the main ...
Foll

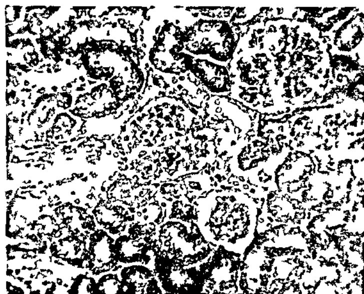


Fig 16 The same on next serial section under a higher magnification to emphasize the irregular course of the fibers

.. of these fibers may be obvious when they reach the media of the afferent artery, they become thicker, irregular and even seem to branch off We never saw them entering the glomerular tuft, they always short circuit it and pass from the afferent to the efferent artery without extending along the capillary bed enclosed in Bowman's capsule, usually they cross the triangular space bordered by the two vessels and the second convoluted tubule (T C II) We first noticed in mouse embryos the fact that nerve fibers followed the basal aspect of T C II between the afferent and efferent glomerular vessels Later on, we had a good opportunity to study the structure of such fibers in one case which we published (1945, [38]) In an adult mouse the juxtaglomerular complex, submitted to silver impregnation could be studied through a series of slightly oblique sections, the branching of two or three main fibers closely applied to the differentiated segment of the tubular epithelium called "macula densa" (Zimmermann) (see p 39), and the res...

ance was obvious, with irre... accounts partly for the m... staining (Masson's trichrome, for instance), another group of these fibrils shows up very clearly after silver impregnation for reticulin (Foot), the basal meshwork surrounding the tubule has a fan like dispersion towards the hilum of the glomerulus

Sometimes, however, the course of the nerve fibers is different, instead of





crossing over the vascular root of the glomerular tuft, they circle around the outer wall of BOWMAN's capsule, passing near the neck of the first convoluted tubule (T C I) and giving off an eventual twig to the capsule itself Afterwards the fibers run along the efferent artery without any remarkable change in their morphology, they follow branches of the efferent artery supplying the renal cortex, where they thin out and fade off between the capillaries and tubules Between capillaries and tubules, the nerves are linked mainly to the former according to our repeated observations, this is in contrast with the situation at the glomerular root where the nerves are closely applied to the basis of the "macula densa"

It should be pointed out that nerves are never found in the medullary area proper, which they do not seem to enter, either from below upwards along the insertion of the calyces (ureteral nerves), or from above downwards with the capillarization of the efferent artery (vascular nerves) This point is remarkable it emphazises the dual embryological origin of the metanephros The ureteral nerves correspond to the ureteral bud growing cephalad to meet the metanephrogenic blastema The metanephrogenic blastema receives its nerve supply from the bundles following the vessels and dividing up all through the cortex The ureteral nerves on one side do not reach the collecting tubules opening into the papillae, the medullary capillaries of the efferent artery, on the other side, do not appear to be followed by nerves Therefore, a sort of "no man's land" exists between the zones corresponding the two main components of the kidney (ureteral bud and metanephrogenic blastema) This territory, apparently free of nerves, is the medullary area proper

The nerve supply to the arteries is inseparable from the innervation of the nephron itself, as a matter of fact, a nephron cannot be considered as a mere tubule, but the neuro-vasculo-tubular unit should always be referred to as a whole From the first part of our description, it may be inferred that so called "secretory" nerves do not exist, in fact, *we never saw fibers ending on or in the* wall of the tubules, although we frequently demonstrated in our sections nerve endings on the vessels, and on the walls of the pelvis, for instance

Spread on the basis of the "macula densa", the nerves come in close contact to the *renal epithelium, the same happens to a lesser degree when they circle* around the glomerulus and pass in the vicinity of the neck of the T C I Oterhwise, whenever a nerve is seen close to a tubular epithelium, it may always be shown to be even closer to a vascular channel of some sort, again, [illegible] walls, *nerves, in our* [illegible] Other a relationship [illegible] a one observers desc[illegible] plexus on each side of the basal membrane with perforating anastomosis, intercellular and intracellular nerve endings of a great variety of shapes, particulary well shown by methylene-blue staining This method is apparently not

reliable, and its results should not be accepted without checking them by other techniques (see for instance HIRT's criticism of the method). Very often after silver impregnation, an impression of intraepithelial nerve ending may be gained, but a closer study on serial sections reveals that the "ending" is but the cut end of a fiber running obliquely between the tubules.

One more word about the aglomerular arteries: in the present state of our knowledge, it seems that they always are the result of atrophy of corresponding glomeruli, consequently their nerve supply is no particular problem.

We found the innervation of the veins much more interesting than expected. The origin of the nervous meshwork situated in the adventitia is the same as the origin of the periarterial plexus, and both networks have such intimate connexions that very often the venous nerves appear as mere twigs arising from more important arterial nerves. The silver-impregnated fibers in the walls of the veins would not be worth any particular description, if their loose network would not be supplied with special endings.

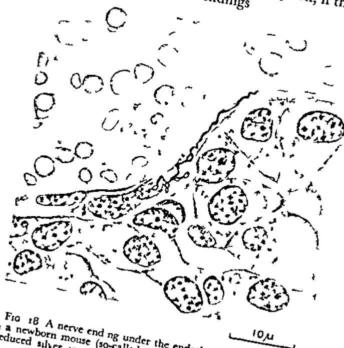


FIG. 18. A nerve ending under the endothelium of a renal vein in a newborn mouse (so-called pressoreceptor type). Reduced silver impregnation. Drawing: oc. 16, obj. 100 mm.

Nerve endings, ring or pear shaped may be found on the outer surface of venous endothelium: they may be isolated or form a sketchy corpuscle,

resembling one of these presso receptors described by Nonidez (1937,[44] 1941,[45]) in the large veins of the cardio pulmonary area.

Sometimes a nerve bundle comes very close to the venous endothelium, sometimes it bulges into the lumen of large veins, covered by an endothelial sheath. These pictures are very clear and the nerve can usually be traced on a



Fig. 19. Intravenous nerve bundle in the inferior vena cava of a 10 mm. mouse embryo. Compare the irregular structure of the intravenous nerves to the smooth appearance of the extravenous fibers in the right lower corner. Reduced silver impregnation. Oc. 16 obj. 100 imm.

few serial sections in new born animals, one wonders if the absence of such formations in adults is not due to the difficulty of following a much longer track in large vessels on a great number of serial sections. Anyway, in young animals such a set-up undoubtedly exists. Sometimes, the nerve bundle does not cross the vein, but goes back to the same side of the wall after running parallel to it. In embryos, an interesting modification appears: in marked contrast with the surrounding nerves, the intravenous fibers are covered with spikes ending with a tiny knob on the inner wall of the sheath, the nerve has the general appearance of a bundle of barbed wire. The sensory value of such an apparatus seems obvious, as no other function may be considered. Compared to other nervous apparatuses elsewhere in the body, it seems hard

to believe that such a definite structure as this one would be without any function whatsoever The same applies to the more important structures that we shall describe and discuss now

We were able to study extensively, in mouse embryos and young mice, intravenous nerve endings, we were fortunate enough to find them later in human embryonic material These endings are of two different types labelled A and B in our previous publications, when A and B are present together they form a complex which we called C In order to give an accurate description of the type A and to make it readily understandable, we better follow its histogenesis as we reconstitute it from serial observations on mice A nerve fiber runs outside the wall of a renal vein, along its course, on a length of several micra, the fibers enlarges and instead of being like a black stripe after silver-impregnation, it shows a bundle of tiny neurofibrils loosened in a pale brown background surrounded by a thin black sheath As the loosening of the neurofibrils and the diameter of the main fiber increase, apparently a similar phenomenon to that so obvious in arteriosclerotic vessels takes place the modified segment seems to increase in length between its two fixed extremities and it takes the shape of a horse-shoe that horse-shoe has always its convexity towards the endothelium, and it bulges into the lumen of the vein, covered by a thin layer of intima, no media being interposed between the intima and the nervous structure The two extremities of the horse-shoe come closer together while its main body bulges more and more in the lumen of the vein up to several micra, the whole horse-shoe undergoes then a process of approximation of its two branches which finally become fused together creating a pear-shaped mass, the dual origin of this mass is suggested by a small hole in its middle due to incomplete closure, or a dark axis running from the pedicle to the middle of the mass of neurofibrils where it enlarges a bit, there are the fused surfaces of

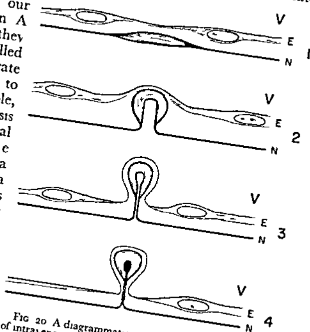


FIG 20 A diagrammatic reconstruction of histogenesis of intravenous nerve endings in young mice For further comment see text
V lumen of the vein E endothelium N nerve fiber

the inner part of the sheath of the horse-shoe At that time generally the bulging has increased and the pear-shaped corpuscle is now related to the main nervous fiber underlying the endothelium by two thin fibers which are sometimes twisted and always surrounded by a very thin film of cytoplasm The modified fiber forming the pear-shaped corpuscle may have a branche, ending

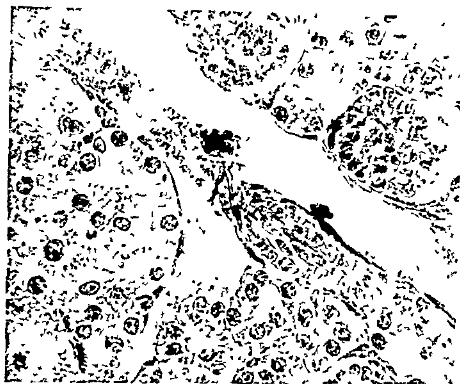


FIG 21 A bunch of intravenous nerve endings in the kidney of a newborn mouse Another group of endbulbs on the left is less clearly defined For the relationship between these and the perivascular plexuses see p 68 fig 45 Reduced silver impregnation (NONIDEZ)

by a little ring, included in the main body of the corpuscle and confusing the picture sometimes Corpuscles of the type A may be isolated but more frequently are found in little bunches of a few units According to variations of silver impregnation or to hazards of orientation of the specimens before section, the type A may appear to differ from time to time from the description given above, although this picture represents the complete corpuscle as usually found under optimal conditions in human material and in mice

The type B is very simple, a branch of a main nerve fiber takes off, usually at right angle, and bulges in the lumen of a vein, covered by a thin film of cytoplasm, it ends by a small knob or ring and may well be the equivalent of

one of the appendages described with the type A Several B endings may be crowded on a small area of the vein, or may be mixed up with a group of A endings forming thus a C complex One more word should be added to this description in a C group one may find various aspects of the above described A formations so that by looking at one complex, one may get an idea of the

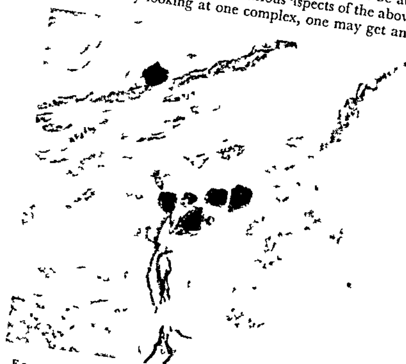


Fig 22A An intravenous nerve ending in the kidney of a 20 cm human foetus the low magnification shows how the end corpuscles bud from the trunk of nerve fibers when these cross a small cortical vein the higher magnification (fig 22B and C) focused on two different planes shows first the intimate structure of the corpuscles then of the pedicle the red blood cells are clearly seen on fig C Reduced silver impregnation

process of differentiation of the whole structure When several fibers bulge into the lumen of the vein in the same area they generally are inclosed in one pocket of cytoplasm and the pedicle is broad the formation being sessile Otherwise as we have said before the pedicle may be long and thin, and the question arises whether many of these endings are not torn from the vascular wall during the various stages of embedding or other stages of the histological technique This may account for not finding sometimes the typical pictures or finding them very scarcely although one sees stumps of fibers crossing the level of the venous wall, and roundish or pear shaped reticulated



Fig 22B



Fig 22C

corpuscles free in the lumen of the vessels We must keep this in mind when we state that we never found any intravenous endings in adults, and remember that successful silver staining of nerves is very difficult to obtain, especially in

the kidney, after the first weeks of life On the other hand, the results are very gratifying during the embryonic stages and the only satisfactory pictures in human material were obtained at the stage of 20 cm

Our series of silver stained mouse embryos being by far the most complete, we were able to study with accuracy on that material what happened to these endings during the early stages of development They appear first in the main trunk of the renal vein and afterwards they bud all over the venous tree when the veins become gradually supplied with nerves Before that renal stage, the nerve endings may be found in the main venous trunks of the abdomen, from which they seem to disappear while they get more and more numerous in the kidney, as if some function was taken over, step by step, by the latter organ Whatever this function may be, will be considered briefly later on, after reviewing data collected on the juxtaglomerular apparatus

We previously alluded to the difficulty of interpreting the nature of nerve fibers according to their greater or lesser affinity for silver salts, and stated that a good test was the existence of an important sheath of myelin or not The existence of myelinated fibers in the renal parenchyma has been a matter of some discussion, we are now definitely convinced of their existence After birth one can find at least one or two of them, even by such





FIG 24 Another subendothelial ending on the same vein the vein is cut obliquely and seems to end blindly on the drawing

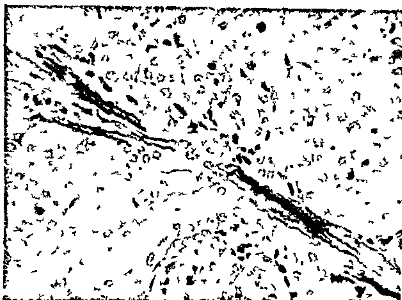
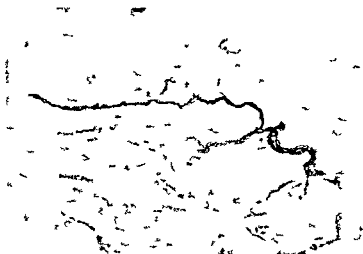


FIG 25 Medullated nerve fibers in the kidney of a young girl In this case the amount of nerve fibers is exceedingly great and every myelin sheath is not stained MASSON's trichrome after fixation in HOLLANDE's fluid



[illegible]

techniques as MASSON s trichromic stain in the large nerve bundles entering the hilum of practically every kidney Their course in the parenchyma has not been ascertained in every case but at least two features are firmly established 1 myelinated fibers follow the branches of the artery as far as the hilum of the glomerulus and may be found lying on the muscular coat of the preglomerular



F G 27 A free nerve end ng in the connect ve tissue between the medulla and the cor ex of the k dney of a 20 cm human foetus The ma n fiber b anches off to the left of the p cture one of the branches (un een here) reaches a lymphat c channel Reduced s l er impregnat on

arteriole 2 myelinated fibers end freely in the connective tissue between the medulla and the cortex of the kidney they loose apparently their sheath and branch off in every direction the last branches showing thickenings at their extremities These fibers are probably sensory carrying impulses from the kidney to the nervous centers The possibility of the preganglionic nature of

the bloodflow throughout the kidney by means of short reflexes the so called axon reflexes in which the subendothelial venous nerve endings may act as receptor endorgans

Wishing to have an over all picture of renal innervation in the classical

sense of the word, and taking into account only the observations which stand beyond any doubt, we are brought to the conclusion that the kidney is very well supplied with nerves, its "reactivity", especially as far as its vascular bed goes, must be a very important factor indeed This impression will be reinforced by the following chapter devoted to the juxtaglomerular apparatus a complex impossible to overlook in any study of renal innervation

CHAPTER II

The normal juxtaglomerular apparatus

THE data presented in this chapter were not collected in the same order as they are given here Study of pathological specimens and of some adult kidneys made it necessary to go back to early stages of development which will be

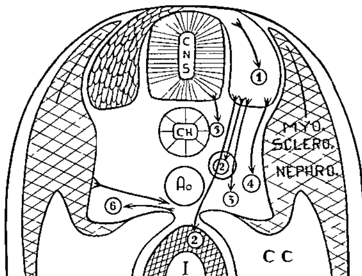


FIG 28 A diagrammatic representation of the derivat ves of the neural crest and the origin of the renal blastema From the neural crest derive
(1)
(2)
(2)
(par
W
ventral root and by (6) the migration of the presumpt ve nephrogenous material

Myo stands for myotome SCLERO for sclerotome and NEPHRO for nephrotome C N S Central nervous system CH Chord Ao Aorta I Intest ne C C Coelomic cav ty

described first
appear norma
are conscious
of our presentation

A transverse section through the lumbar region of a mammalian embryo, before the first appearance of the renal blastema, shows the neural crests arising from the neuro-ectodermic angle and bulging ventrally Besides the ganglionic cells of the dorsal roots, the material of the neural crest gives rise to the sympathetic ganglia, the paraganglionic cells such as the medulla of the suprarenal, and SCHWANN-cells, but a close study of the lower limit of the neural crest reveals that some of its cells undergo a mesenchymatoid transformation and become quite similar to pure young mesenchymatous cells present in that region This suggests the existence of an ectomesenchyme or mesectoderm, lateral and ventral to the spine, in the abdominal area, as exists in the cephalic part of the embryo

Definite proof of the existence of a cephalic mesectoderm has been given by various authors, and its fate has been studied very accurately It is known to give rise to connective tissue, cartilage, etc (STONE, 1922—1929, [84, 85]) (VAN CAMPENHOUT, 1931—1937, [9, 192]) HILBER (1942, [100]) demonstrated by his experiments on amphibians (Trito, Bombinator) that the neural crest in the *truncal area becomes mostly mesenchymatous and migrates caudally, giving* rise to a typical mesectoderm of neurectodermic origin

GRUENWALD (1939, [86], 1943, [83]) concluded from his studies of the differentiation of the metanephros, that nervous tissue may induce a mesonephric-like differentiation of the metanephrogenic blastema in the chicken embryo VAN GEERTRUYDEN (1946, [199]) pointed out that nervous tissue may induce the production of nephrons by the mesonephrogenous blastema in the absence of the ureter, (which induces it normally) He showed that the mesonephrogenous material migrates to and fro between the nephrotome and the mesenteric root, where the neurectodermic elements migrate at the same time The lumbar ectomesenchyme may thus contribute to the constitution of the renal blastema The induction by nervous elements of a differentiation in a renal anlage may be linked to the presence of a neurectodermic material

In the lumbar region where ectomesenchyme would be present, the renal blastema appears at a later stage The ureteral bud growing cephalad out of the pelvis, encounters this mass of mesenchyme composed of young cells closely packed, and divides it up by branching regularly in the same way as the bronchial tree (LUDWIG, 1949, [23]) As we recalled previously (p 12) the small balls of blastema isolated on each side of the ureteral branches undergo several changes a lumen appears, to form vesicles which become rapidly S shaped, the lower curve of the S is the anlage of BOWMAN's capsule and its upper end includes the "pars intermedia" or junction between the nephron (or true renal unit) and the collecting system A close study of the differentiation of the nephron, points to two facts which are of definite importance very early a vascular lumen appears in the concavity of the lower branch,

their broad end, and those cells close to the base stand on an early basal membrane by an enlarged foot While the tube stretches and becomes more and more twisted, the epithelium progressively gains its adult appearance,

glomerulus, maintains its embryonic appearance, in contrast to the neighbouring segments It resembles a young neuro epithelium It is not unusual to find in relatively early stages a discrimination between two types of cells some are swollen, roundish and of a light shade of pink, others are red and taller, with an enlarged upper extremity bulging in the lumen of the tubule, with a narrow junction at its middle and lower thirds, and an enlarged foot resting on the base of the tubule These more or less hour-glass shaped, acidophilic cells, generally border on both sides a clearer cell, their curvatures fitting its ovale shape Differentiation will now proceed until it becomes very obvious in certain adults, where we noticed it first

In the mean time, the glomerular tuft develops It has been shown by DE WINIWARTER (1943,[49]) and confirmed by us that the endothelial channel enclosed in the early BOWMAN's capsule becomes surrounded by mesenchymatous cells which very early assume an epithelioid appearance, this primary vessel is thus an artery, and the same appearance is easily found early in the development of any renal artery, as in arteries elsewhere The inner layer of BOWMAN's capsule, at this stage, is represented by a columnar epithelium in striking contrast with the outer layer which is very early flattened out and endotheloid The inner layer begins then to show folds, in which expansions of the primary artery grow, giving an early and sketchy picture of the glomerular tuft An interesting point is that the epithelioid cells surrounding the primary artery maintain their appearance for a very long time while similar cells all over the arterial tree in the kidney gradually differentiate into smooth muscle cells, a process which eventually takes place in the glomerulus itself later on Undoubtedly, the muscular coat, or media, of these renal arteries is originally composed of cuboid cells appearing epithelioid in sections These epithelioid cells of the glomerular artery remain embryonic and in close contact to the tubular segment which remains embryonic too Further differentiation gives every reason to believe that these embryonic looking structures represent the "anlage" of the juxtaglomerular apparatus which thus may be

distinguished from surrounding material ever since the early stages of development.

The full details of this process have already been published in a paper (1948, [40]), in which we pointed out how uneasy it was to give precise chronological landmarks for these phenomenons, as they happen over long periods of



time in the successive generations of nephrons which develop inside the kidney during foetal life Obviously they will be present more often at the periphery of the kidney than in the depths of the parenchyme where the older generations are located, this may explain, to a certain extent, the presence of the modified muscle cells, in the adult kidney, usually in the outer half of the cortex, although an alternative explanation may be afforded by relating their appearance to a peripheral decrease in blood pressure; (see p. 70 and sq.).

As we said before, the epithelioid cells of the glomerular artery finally become smooth muscle cells On the other hand, the juxtaglomerular segment of the renal epithelium may be found undergoing a more pronounced differen-

tiation By this time it is obvious that this segment belongs to the second convoluted tubule and represents the so called "macula densa' (ZIMMERMANN, 1929,[2], 1933,[22]) Obviously the "macula densa' or '*palisadic segment*' differentiates before the nerves reach its vicinity

In the later half of foetal life and after birth very definite changes may be



Fig
young
n the
coated
macula densa with a vacuole under one of the dark cells the efferent arteriole is in the upper part of the picture (MASSON's trichrome)

seen in the macular epithelium, although in some cases they are not evident A remark should however be made in order to get the best results and the clearest pictures, fundamental rules of a sound histological practice should be applied which are too often overlooked when surgical or pathological speci

cells may extend beyond the limits of the macular segment, but it reaches its highest degree on this particular spot The presence of so called "vacuoles" makes the picture a bit more confused, these vacuoles appear in the basal part of the macular cells, and were noticed by various authors A close study on serial sections reveals, however, that if the existence of vacuoles is possible, it



trichrome

is also frequently possible to trace the origin of the so-called "vacuoles" to the lumen of the T C II, with which they are connected by small intercellular channels, being thus true diverticula of the lumen of the tubule These tubular processes are usually located between the main body of acidophilic cells and their basal expansions The narrow intermediate parts of the cell bodies are lateral to the diverticulum and the whole picture represents some sort of a bridge like structure which reminds us of the epithelium of CORTI of the inner ear Between the acidophilic cells (A) one finds ovoid cells (B), less slender than the previous ones, and resting in alveoli build by the fuchsinophilic elements Comparing further these two types of cells, the cytoplasm of the A cells with its closely packed, extremely fine, red granules looks more like an homogeneous mass, *in the middle of which a dark staining nucleus assumes the* same shape as the upper half of the cell In the B cells, the granules are coarser and diluted by a mass of clear watery fundamental substance in the middle of which floats the nucleus, this nucleus is generally round and clear, but

sometimes sickle shaped on sections and excavated in the fashion of a bowl In this case, the concavity of the nucleus may be facing a vacuole, by far the most frequent in a basal corner of the cell (or between two cells) The study of various aspects of these clear cells conveys the impression that in some cases they

leavi

betw

suggests that the B cells are only an oedematous form of the A type Mc MANUS (1943, [126] & 1944, [129]) claimed that in the cat and rabbit's kidneys the GOLGI structures seen as granules and short rods are on the side of the nucleus facing the attached pole of the cell, in the macula densa, although the usual position is immediately on the lumen side of the nucleus in the distal tubule This would be an useful indication of the individuality of this segment if JASSWOIN (1925, [106]) and FISCHER (1938, [66]) had not described variations of the GOLGI apparatus according to temporary functional states, in various parts of the nephron, and if the process of differentiation described above did not precisely imply functional changes, in contrast to a resting stage where all the cells appear more or less the same It is not an artefact due to inadequate fixation and staining, because every cell in the vicinity looks perfectly normal in keeping with admitted standards of health Moreover this differentiation is prepared step by step throughout embryonic life It is more frequently found in cases where functional disturbances of renal hydro or hemo-dynamics may be suspected and it undergoes definite changes in pathology

We may conclude this description While the nephron differentiates, two juxtaglomerular structures undergo particular changes the "macula densa"

become quite similar to components of a normal "media", but they remain capable of taking anew an epithelioid structure The macular cells show a definite tendency to divide up into two morphological types which may be only two different functional stages It should be remembered that these structures are in close contact with the nerves described in the previous chapter The relationship between artery, modified muscle cells and nerves has given birth to a new concept the "neuro myo arterial" juxtaglomerular apparatus (GOORMAGHTIGH 1932 [76], 1944, [78]) This apparatus with the macula densa forms the juxtaglomerular complex (Mc MANUS, 1942, [124] [125]) The arterial muscle cells and the macular cells derive from the mesenchymatous "anlage" of the renal blastema, which may have a neurectodermic component, or mesectoderm The chapters to come give us more information on a possible link between the juxtaglomerular complex and mesectoderm

CHAPTER III

Comparative anatomy

We shall summarize here very briefly observations made on kidneys of various animals The facts thus pointed out have a direct bearing on our study

A Alligator lucius

In the vicinity of the hilum of the kidney, the aorta the main renal arteries and some of their branches entering the parenchyme, show suggestive features

The media of the larger vessels consists mainly of a circular coat of smooth muscle cells on the ventral side of the aorta and in the renal area the myocytes on one side change their main orientation and instead of being concentric to the vascular lumen, take a stellate arrangement and bud into the outer layer of connective tissue While undergoing this change in position, they modify their structure and become larger, clearer and granular, where granulations appear myofibrils vanish (fig 32, A & B)

They assume thus a definite epithelial endocrine appearance and form small islets in the outer layer of the adventice, resembling closely paraganglionic cells In the vicinity of the arteries where such a process takes place small groups of cells exactly similar to these come in close contact with other epithelial masses the cytoplasm of which is packed with tiny little granules giving a much darker appearance to the cell These complexes are surrounded and pervaded by nerve fibers and the darker epithelial cells may be found mixed up with typical ganglionic cells

The significance of the whole process may be expressed as follows smooth muscle cells of the media migrate to the periphery and undergo an endocrine differentiation, exactly similar cells are found in the vicinity of these arteries as a component of epithelioneural complexes of a paraganglionic type This strongly suggests that smooth muscle cells have a paraganglionic potentiality, the question arises whether these cells have a mesectodermic origin (neural crest) which would be the only satisfactory explanation in the present status of our knowledge

So far no experimental answer has been given to this question but several observations are of interest and they all point to the same direction The existence of a lumbar ectomesenchyme in the renal area, is highly probable [illegible] d es n mammals have shown that the muscle coat of

glomerular apparatus or may be reprodu [illegible]



FIG 32A The hilum of the kidney of Alligator Lucius showing the budding of periarterial myocytes in the outer layer of the artery (Low magnification) MASSON's trichrome

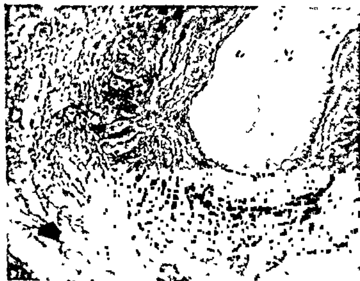


FIG 32B The same under high magnification

logical evidence of secretory activity such as that of the granular cells of the renal arterioles of the mouse.

B. Other vertebrates.

The hilum of the kidney of *lower vertebrates* (frog [1], salamander, turtle, a.s.o.)



Fig. 33 The macula densa in the kidney of a frog, at the vascular pole of the glomerulus, with a definite palisadic arrangement. Masson's trichrome.

and its exp...
number ... most of them representing the med... of the suprarenal, but some of them not (clear cells, when opposed to dark ones filled with iron staining granules). There is nothing new about

[1] The frog kidney has typical macular structure ... Muylder, 1950, 43) ... with a meso- or m... relationsh...



Fig 34 Two groups of paraganglionic cells along the intrarenal vessels of the turtle the cells are overloaden with iron staining granules Masson's trichrome

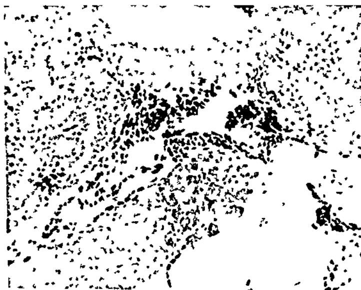


Fig 35 In the renal hilum of a rooster paraganglionic cells with dark iron staining granules accompany nerve cells along the renal vessels Hemalum Eosin

this observation (see, for instance, DA COSTA, 1939,[3] and the monograph on the adrenal gland by HARTMAN and BROWNELL, 1949,[94])

The same observation may be made in *birds*, as we did in the kidney of a rooster, typical paraganglionic neuroepithelial bodies were present even in



FIG 36 A nerve cell in the kidney of the carp embedded in a nerve running alongside a large vein this is a very common feature in the kidney of old carps MASSON s trichrome

the midst of the parenchyme along the renal arteries (dark granular cells), besides we found at least one picture suggesting the type of transformation described in the alligator

The aorta and the kidneys of various *fishes* are of great interest GERARD (1943,[74]) reported on glomic structures in the aortic wall of various TELEOSTEI

(Lepadogaster Gouanii, Lepadogaster Candollii, Callionymus Lyra) when it gives off the pronephretic arteries We described (1950, [42]) a neurovascular complex of a glomic type in the kidney of the carp (Cyprinus Carpio) a great many nerve cells may be found along the vessels (arteries and veins) (see fig 36) The aortic wall may show another type of glomus like structure which



FIG 37 Modified muscle cells nested in the wall of an abdominal artery of the carp at the inlet of an arteriovenous anastomosis MASSON'S trichrome

emphasizes the importance of this region for the general regulation of visceral blood supply

There is a definite possibility that muscle cells of the arterial wall, in the renal area at least, have an endocrine potentiality and form epithelioneural bodies Their link with the sympathetic nervous system would be best explained by their mesectodermic (neural crest) origin, and such an origin is, at least, possible from the morphological standpoint

A nervous origin of muscle cells is not surprising as the muscles of the iris derive from the peripheral part of the retina which is an expansion of the central nervous system These muscle cells are smooth in the mammals and striated in birds They have been compared to the epitheliomuscular cells of the Coelenterata From our viewpoint no difference should be made between striated muscle cells and smooth muscle cells as we remember the structure of the human oesophagus, or the smooth and striated muscle coats of the intestine of the perch, for instance

One of the two types of muscle cells is not unfrequently found in close

relationship to nerve cells, as in cerebellar tumours, nerve sheath tumours and renal tumours where they would originate from the same stem, in MASSON's opinion

"In so far as the reality of the genetic relationships between muscle and nerve tissue is concerned, different facts argue in its favor in the *same fashion* as do the renal adenosarcomas There in first of all MARINESCO and GOLDSTEIN's myogenic "medullo-epithelioma" of the cerebellum, which could very *well be a complex* nervous tumor–at the same time medullo-epithelioma and neuro-epithelioma of the cranial crest–included within the cerebellum Next there are the observations made on rhabdomyomas of nerves (GRATIA, ORLANDI, P MASSON), whose striated cells come not from myotomes but from constituents of nerves originating from the neural crests" (MASSON, 1938,[132], p 31)

SZANTROCH (1938,[184]) in his studies on the development of the sympathetic nervous system expresses the opinion that one single blastema gives rise to the sympathetic ganglionic cells and the muscles to be innervated through the expansions of these cells, in the digestive and respiratory system and the *abdominal blood vessels More recently* KEUNING *(1945,*[113]*) admitted that* the vegetative nerve plexus of the intestinal wall was of mesodermic origin WEBER (1940,[203]) admits that the vegetative neuroblasts along the intestine are at the beginning undistinguishable from pure mesenchyme cells, but, among the anonymous mesenchyme cells, are a great many ectomesenchymatous elements whose migration from *the neural crest is indisputable* VAN CAMPENHOUT (1931,[191]) demonstrated by experiments on chicken embryos that no development of intravisceral (digestive) nerve cells could be expected without migration of sympathetic neuroblasts originating from the neural crest Nerve cells seem to differentiate from mesenchyme in the lungs (BAUMANN, 1940,[7]), again, *they may be mesodermic or mesectodermic,* although we don't have any hint to the existence of an ectomesenchyme in this particular field

The same general reasoning applies to the periarterial blastema which we are discussing now. not only does this blastema give rise to modified muscle cells *which sometimes* take a neuroendocrine appearance, but cells have been described which extend in the arterial wall the nervous networks themselves (CAJAL's interstitial cells, see the recent studies by BOEKE, 1940,[19], 1943,[20], 1949,[21]), not to speak of their presence in intestinal musculature *The main* trouble with these cells is that their nervous nature or "neuroid" quality still rests upon their silver impregnation more than on their specific morphology, their true significance is controversial Our observations on the arterial wall of Alligator are less open to discussion

The modified muscle *cells of the renal arteries* have been compared to the glomic cells described by MASSON and even to the cells of the His-bundle

Both cells are in fact m...
specialized in the
elements such as g...
relationship of the ...
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a ... muscle cells in the chain of events is
...herent, whether they secrete an hormone or pass over a ner-
vous impulse, has no bearing on our discussion The interpretation of our
observations seems reasonable in view of the known facts myocytes of the
arterial media become endocrine, and migrate to join neuroepithelial bodies
A sensible way to explain this, is to postulate the presence of ectomesenchy-
matous cells in the periarterial blastema as we said at the beginning of this
discussion

An extensive review of glomic structures in the sense of MASSON (19...)
and specialized arteriovenous anastomoses as de...
(1938, [71]) would be out of pl...
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... (see for instance ... terms of function ... ons are not purely
... FRANKLIN and MC LACHLIN, 1936,[68 & 69], ... (local regulation of
BONIVENTO and MORIN, 1941,[22] TRUETA & al., 1947,[87])

CHAPTER IV

Possible relationship between nervous elements and some aspects of renal pathology

A NEPHROSCLEROSIS

A slow but continuous process of nephrosclerosis decreases the number of glomeruli ever since the first completion of development of the kidney Later on, in adult life, this process increases in activity and may finally result in gross impairment of renal function, by this time it has become a clinico pathological entity because its ill effects are obvious

The picture of renal tissue undergoing sclerosis is very much confused We have studied it very carefully, and, after checking our observations by com paring them to several descriptions found in the literature, we think we are on the way to the understanding of this problem

To begin with, derivatives of the ureteral bud do not seem to play any im portant role in the picture of nephrosclerosis We are thus left with the tubulo vascular unit to which we referred previously and which corresponds to the metanephrogenic blastema The scarring of the glomerulus seems to initiate the whole process The shrinkage of the glomerular tuft, surrounded later by a fibrotic capsule and finally replaced by it does not always result from a serious impairment of blood flow through the glomerular arteriole, this is shown by several observations of aglomerular arteries, which are indeed nephronic vessels, the glomerule of which underwent sclerosis although the main channel remained patent Such observations postulate an intraglomerular mechanism depriving the capillaries of their normal blood supply and producing their collapse We don t see any intraglomerular nervous penetration, but we know that the capillary channels are embraced and supported by a skeleton of ROUGET
ter is ob c
elements c
carp, its action may be compared, although in a more localized fashion, to the function of the muscular intraglomerular vessels of the SELACHII (BARGMANN 1937,[6])

At the same time, the tubules do not disappear right away after their glome ruli have been reduced to an afunctional fibrotic mass, indeed they show de finite signs of hypertrophy and even increased cellularity (true hyperplasia) which gives the whole picture a tumor like appearance

Related to the previous point is the fact that the surviving epithelial cells show signs of excretion or secretion, they have intracytoplasmic granules and vacuoles, as active glandular cells do, also masses of an hyaline substance are

enclosed in epithelium lined vesicles comparable to a thyroid like arrangement Finally, debris are found apparently trapped in a tubular segment without connexion with the collecting system Several observers endeavoured to explain the significance of these pictures according to a probable function of the sclerotic kidney the endocrine secretion of the kidney has very often been referred to in connexion with these aspects One should not forget that two processes at least may be present and that the masse of secretion products surrounded by epithelial cells may well be remnants of the excretory function of the tubules, whereas the eventually so important endocrine function may not be shown by any striking morphological changes The process of nephrosclerosis may have two different outcomes one is complete shrinkage of the kidney when atrophy is predominant the other produces local hypertrophy and results in tumor like productions the so called adenomas true adenomas and possibly, malignant tumors see § D

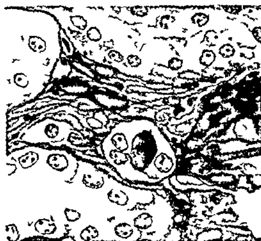


Fig 38 A free tubular segment human nephrosclerosis to show the colloid like substance in the lumen of the little vesicle Masson chrome Drawing or 6 obj 10 mm

B THE RENAL NERVES IN NEPHROSCLEROSIS

WE have already mentioned the renal nerves and their eventual action on micro *muscular sphincters Two points are of interest first, no more than in normal* kidneys did we e
kidneys second
as a rule always
tration nor does the silver impregnation reveal any gross pathology (the remarks made p should however be borne in mind) Sometimes one gets the impression that the nerves increase in number this should be related to a decrease in the mass of renal parenchyme which dilutes them Many normal nerves are thus seen in a fibrotic shrinking scar and this might well be kept in mind by physiopathologists (fig 39)

C THE JUXTAGLOMERULAR COMPLEX IN NEPHROSCLEROSIS

WE shall consider the second convoluted tubule with the macular area and the muscle cells of the glomerular arterioles

1 The second convoluted tubule

We have already discriminated between the behavior of the glomerulus, the convoluted tubules with Henle's loop, and the excretory portion proper In relation to the object of our study, it is, of course, interesting to try and find out whether the portion of the nephron extending between the glomerulus

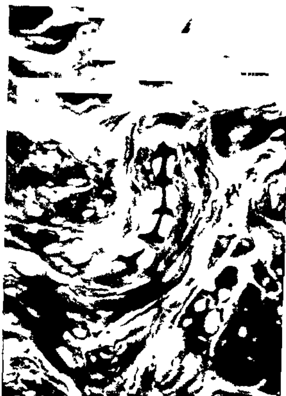


Fig 39 Medullated nerve fiber in a human atrophic kidney, to show the funnels of Golgi (high magnification) Masson's trichrome

and the "tubuli recti", degenerates uniformly, or if some segments react in a more or less typical way, different from the neighbours

There is some recent evidence that more segments should be individualized in the nephron (on various grounds, morphological and functional) than the classical subdivisions 1 The first convoluted tubule with a neck, various loops and a terminal straight portion, 2 Henle's loop with a narrow and broad branch, 3 second convoluted tubule with a "macula densa" and a terminal "pars intermedia" Further subdivisions of this complex are suggested by researches pertaining, for instance, to the appearance and behavior of fat-free

and fat loaded segments, to the shape of cell-borders, to the intensity of athrocytosis, to the capacity of iron storage, etc

Whatever the final picture of the normal adult nephron will be, when the renal tubule undergoes sclerosis it does not react in the same way on its full length Very good evidence of this has been presented by several investigators and we should like to quote here some results of OLIVER and co workers (1934, [53], 1950, [54])

The first convoluted tubule (T C I) is subjected to great variations it may undergo atrophy and fatty degeneration, or become dilated, hypertrophic and hyperplastic with an increase in its length and its degree of convolution, between these two possibilities exist all transitional stages and, even more, marked atrophy and marked hypertrophy may be found alternating along the course of a single unit HENLE s loop is not the site of hypertrophy or hyperplasia The second convoluted tubule (T C II) is usually dilated and irregular enclosing in its lumen a coagulum, or fatty or granular "debris", it may also contain crystals (as the loop of HENLE sometimes does too) At the distal end of T C II, the 'pars intermedia' (connecting tubule or 'Schaltstuck') is usually empty and non dilated A very important point is that the renal unit undergoes fragmentation which is particularly obvious in certain regions "When the deeper layers of the cortex and the outer stripe of the outer zone of the medulla are dissected, among the hypertrophied and hyperplastic terminal spiral portions of the proximal convolution, are found isolated segments of tubule, the external contours and general configuration of which resemble exactly those of the intact enlarged kinked spiral They are obviously interrupted or pinched fragments of this terminal portion of the proximal convolution, for they may be found lying in situ arranged in a linear series, each unit closely following the other' OLIVER & LUEY (1934, p 807)

The abnormal kidney may show glomeruli without connexion with the tubules and, in tubules separated from their glomeruli, tubular segments disconnected from each other, undergoing atrophic, hypertrophic or hyperplastic changes in their epithelium, with a normal, narrowed or enlarged lumen Cysts may be formed with a colloid like substance "Such vesicles and cysts are of course, functionless and in certain cases may comprise a considerable part of the epithelial-tubular element of the diseased organ' OLIVER & LUEY (1934, p 815) On the contrary tubular hypertrophy and hyperplasia may be related to a compensatory mechanism, the renal epithelium taking over some functions of the glomerulus as in the aglomerular kidney of lower vertebrates This phenomenon should be kept in mind while trying to understand such changes as described by SELYE and STONE in the so called endocrine kidney of rats (1946, [75]) The changes occuring at the level of T C II, with particular reference to its terminal portion, were the main object of our study The absence of spectacular cellular reaction may be due to either a

disposition of vascularization protecting this area from the full impact of blood non-purified by a preliminary filtration through the glomerulus (this blood being partly purified by the compensating T C I), or by a special function of this segment which would not take up toxic constituents from the blood The latter hypothesis which suggests a special metabolism of this segment is supported by observations of elective lesions, in such cases as localized nephritis and crush-syndrome Both mechanisms may be involved Wherever the true explanation lies, the epithelium of T C II remains fairly normal in nephrosclerosis and when other sections of the tubule eventually degenerate and disappear, the second convoluted tubule generally survives

Though its epithelium does not undergo the changes quoted above, it is nevertheless subject to cytological modifications It should be remembered here that the T C II, particularly in its terminal portion is not homogeneous Several observers pointed out that the epithelium of the T C II shows two types of cells, dark ones and clear ones One might suggest that these two types are basically similar, and represent only different stages of activity, but this does not lessen the importance of the difference which may be very striking indeed As said previously such a difference is more pronounced in the macular area The chief features of that heterogeneity were described in a previous chapter but we want to add here some more information

Wigert and Ekberg (1903,[206]) demonstrated the existence, in the renal epithelium of the frog, of two different cellular types dark principal cells with a narrow base and a broad upper extremity, and clear intermediate cells nested in the alveoli formed by the dark ones, with an expansion of the lumen in their own cytoplasm

With Da Fano's silver staining technique, Okkels (1929, [51]) demonstrated in a series of animals (rabbit, dog, rat, pigeon, frog) renal cells characterized by their affinity for the silver, and bulging into the lumen of the tubule Feyrter (1940,[64], 1943,[65]) made a similar observation and extended it to other groups of cells found in the vicinity of the T C II These cells would be similar to the "Schaltzellen" (Schachowa) which are the darker cells found in the end segment of the nephron extending under the base of the nearby clear cells, with their own broad base

When the nephron disintegrates, the end segment and especially the macular segment survive thus for a long time The study of a series of human kidneys undergoing sclerosis established this fact Practically always nephrons can be found degenerating in otherwise healthy looking adult kidneys and portions of nephrons surviving between the normal tubules may account for these epithelial masses or vesicles eventually found scattered throughout the kidney Other explanations may account for the presence of such structures one is their differentiation from embryonic cells of the renal stroma, much in the same way as Leydig-cells do in the testicle, but our studies of histogenesis of the

kidney never provided us with any evidence to support this hypothesis, another one assumes their origin to be in the wall of the arterioles which would be more or less the same hypothesis as the previous one (see p 71), another hypothesis still sees their origin in detached appendages and diverticula of the renal tubule itself (PETER, 1907,[157], FEYRTER, 1940,[64], 1943,[65]), here again, the



histogenesis of the nephron does not give much support to this hypothesis, unless one admits that these appendages do not appear clearly before the adult stage, at what time they may as well be considered as a first symptom of the hyperplastic reaction mentioned previously This relationship to the ageing of the nephron and its eventual breaking down seems thus to be probable Whatever their origin is, the most conspicuous of these islets resemble closely the T C II and

FEYRTER also de

droplets and va

itself, he thought that these islets where a diffuse endocrine organ of the same nature as the cortex of the suprarenal These islets are obviously the same as the cell masses described previously by BECHER (1936,[9], 1937,[10], 1949,[2]), in the vicinity of the vascular pole of the glomerulus, although BECHER thought that these cells where more similar to the medulla of the suprarenal To sum up we believe that these cells are mainly derivatives of the T C II and an expression of a slow process of breaking down increasing in intensity as time goes on

The segmental survival of the nephron is quite typical in the macular area This has been noticed by GOORMAGHTIGH and the conclusions of our observations are in complete agreement with his, in cases of polycystic kidney and renal atrophy the few tubular remainders scattered through a fibrous mass had often the structure of the heterogenous macular segment, showing thus its definite tendency to survive while the rest of the kidney disappeared We made the same observation in the extratumoral zone of the renal parenchyme, in a mixed tumor of the kidney to which we shall refer later on

These two last cases are good illustrations of what may happen in nephrosclerosis Of course if nephrosclerosis is bilateral, the patient will die before ultimate stages of fibrotic scarring occur, but unilateral cases give us the opportunity to observe a disease of long standing On the other hand the proliferative activity of the hypertrophic stage may increase and give rise to benign tumors (adenomas) and eventually malignant tumors (renal cell carcinomas)

2 *The muscle cells of the glomerular arterioles*

WE have already said a word about the origin of the aglomerular arteries and their relationship to a shrunk glomerular tuft A glomerular artery may also disintegrate the same way as any tied off artery does when no collateral channels



FIG 41 In the kidney of a dog the juxtaglomerular complex is represented by a macular segment of T C II (above) and a pseudo-MEISSNERian corpuscle (below) this corpuscle belong to the walls of the afferent and efferent arterioles where they give off their branches to the glomerular tuft MASSON's trichrome





develop But nowadays it is impossible to sum up so briefly the situation RUYTER (1925,[167]) was the first to describe, with some details, the modified muscle cells of the media of the preglomerular arterioles in several animals *they were epithelioid and characterized* by the presence of granules staining black with iron hematoxylin, remaining unstained by the dyes for lipoids and glycogen, but being well stained by VAN GIESON's technique after mitochondrial fixation Sometimes these granular cells *contain myofibrils, proving* their muscular nature Similar findings in the human kidney were described by OBERLING (1927,[147], 1944,[148 149])

Since then several people have published the results of their researches on this subject Modified muscle cells were described by OKKELS in the mesonephros of the frog (1929,[152])

GOORMAGHTIGH (1932,[76] to 1944,[78]) made similar observations on the kidneys of human beings and a cat He mentioned the relationship of the modified cells with nervous fibers and gave a description of a "pseudo-corpuscle of MEISSNER" buried in the angle of the afferent and efferent artery, this "pseudo-corpuscle of MEISSNER" has *unfortunately been the source of* much confusion, although it was said to be composed of more or less spindle-shaped cells resembling the SCHWANN cells, piled up in the corner of the vascular root of the glomerulus Such an appearance is not unfrequently seen, but after observing it closely, times and again, we were absolutely unable to detect anything suggesting the nervous nature of this structure, on the contrary, it very closely resembles these micromuscular bundles that we observed along renal vessels of the carp Such micromuscular bundles exist also around the ampulla at the origin of the glomerular loops, a fact mentioned also by GOORMAGHTIGH (1941,[77]) This author calls the complex "segment neuro-*myo arteriel" and suggests that it would* act as a sensory zone from where vasomotor reflexes would originate regulating the blood flow through the glomerulus

ZIMMERMAN (1933,[212]) who was one of the authors who first described the macula densa, described also a "polkissen" which really seems to be the same thing as the modified muscle cells [see also HERINGA & RUYTER (1933,[96]), MATHIS (1934,[34]), MONSERRAT (1934,[135]), KAUFMANN, 1940,[109])]

BECHER (1936,[9], 1937,[10 11], 1949,[12]) found the modified muscle cells too, but his main interest was focused on small islets of clear epithelial cells in the vicinity of the afferent arteriole he thought these islets were endocrine, similar to the medulla of the suprarenal and secreting an hormone wich produces the congestion of the modified muscle cells of the arteriole He did not believe that these islets were deriving from the tubules themselves, he stated that these islets had not been described before except by GOORMAGHTIGH who called them "pseudo-corpuscle of MEISSNER" not realizing their real nature

CLARA (1936, [26]), (1938, [27]) described also the modified muscle cells, the neighbouring epithelial islets and, in the hilum of the glomerulus, a sphincter of small smooth muscle cells. APPELT made similar statements (1939, [3]).

More is to be said about the modified muscle cells of the media. Although some pathologists believe that the epithelioid cells are a degenerative form, without function, of arteriolar myocytes, a large number think that they probably have a function related to the blood flow through the glomerulus, but how this works out is a matter for conjecture. For some authors these cells represent the most peripheral link of a sensory mechanism such as in the glomic structures and are the origin of the afferent pathway of a reflex arch. Some other observers think that these cells are apt to become oedematous and occlude the lumen of the afferent artery (QUELLZELLEN).

Finally, GOORMAGHTIGH made an interesting contribution to this problem; he reproduced GOLDBLATT's experiment on several animals and noticed with the onset of hypertension an hypertrophy and hyperplasia of the smooth muscle cells. His observations suggested that the modified muscle cells are taking a definite secretory appearance. He thus concluded that the hypertensive hormone was secreted by the modified muscle cells which he called C.M.A. = "cellules musculaires afibrillaires".

Several investigators undertook to verify this hypothesis by experiments on animals, or by observations of normal human kidneys and kidneys of patients suffering from high blood pressure. Examples of such researches will be found in the papers by GRAEF (1940, [8], 1943, [82]), GRAEF and PROSKAUER (1945, [83]), DUNIHUE and CANDON (1940, [54]), DUNIHUE (1941, [55], 1946, [56, 57]), KAUFMAN (1941, [10], 1942, [111]), MC MANUS (1942, [124], etc.), FRIEDMAN and KAPLAN (1942, [70, 7], 1943, [72]), FRIEDMAN, KAPLAN and WILLIAMS (1942, [73]), OBERLING (1944, [48, 149]), SCHLOSS (1945, [170], 1946, [171], 1947, [72], 1948, [173]), DE MUYLDER (1946, [39]), DES PREZ (1948, [44]), DINA, BERNASCONI and MARTUZZI (1950, [50]), etc.

The complexity of the problem will be appreciated by taking into account the hypertrophy of the modified myocytes after bilateral sino-carotidal denervation resulting in high blood pressure (ELAUT, 1934, [60]), or by the administration of adrenotrophic hormone or desoxycorticosterone (DOUGHERTY, 1948, [53]).

For the time being it is very difficult to decide which hypothesis is the right one, and whether the C.M.A. might not have several functions altogether. These cells are undoubtedly present in nephrosclerotic kidneys but it is difficult to decide whether their number is significantly increased even in some cases with definite high blood pressure.

To sum up this section on nephrosclerosis, we shall say that the glomerular hilum shows various structures, forming part of a juxtaglomerular complex, some of them getting conspicuous only through senescence.

1 The afferent artery with normal smooth myocytes and modified epithelioid muscle cells

2 The efferent artery, the structure of which may approach that of the afferent artery

3 A micromuscular sphincter at the inlet of the glomerular tuft

4 Nerve fibers running along the arteries and crossing the space between the base of the macula densa and the vascular root of the glomerulus

5 The macula densa of the T C II

6 Free epithelial islets, deriving apparently from the T C II

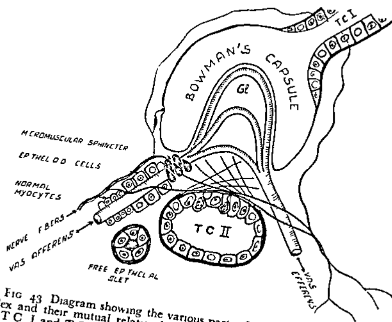


Fig 43 Diagram showing the various parts of the juxtaglomerular complex and their mutual relationship

T C I and T C II stand for first and second convoluted tubule respectively

The disappearance of the elastica interna where the epithelioid cells are present has not been shown to avoid confusing the picture

The next chapter will possibly enable us to go further and see whether there may be a relationship between 5 and 6, and the nervous system

D Neoplastic processes in the kidney and neurogenesis

Hypertrophy and hyperplasia accompany nephrosclerosis, mimicking thus closely hepatic cirrhosis In the same way as regeneration in cirrhosis produces adenoma-like structures, pictures are present in the nephrosclerotic kidney suggesting the production of renal adenomas True renal adenomas may also

be found, and their growth may produce in the surrounding tubules nephrosclerotic changes The question whether true adenomas surrounded by nephrosclerosis, and nephrosclerosis producing adenomatous pictures are closely linked, is open to discussion The relationship between true or pseudo-adenomas on one side, and malignant tumors of the kidney on the other side is also a matter of much disagreement Large series of cases, studied from that point of view, were published without presenting any clearcut evidence, however the general trend seems to be that an hyperplastic reaction may give rise to true adenomas and that true adenomas may undergo malignant changes, although adenomas may be found in normal looking kidneys and large adenomatous masses may be present without showing any malignant transformation

All this, of course, concerns only the tumors arising from the nephron itself, exclusive of the collecting system (renal cell growth or metanephroma) They present various aspects and the pathologists experiences a lot of trouble in trying to classify some of them

The possible relationship between free epithelial islets and hypernephroma should be closely investigated The following pages will show us that the typical hypernephroma is probably a well characterized, highly differentiated renal tumor We know that three types of cells are set free in the kidney to form adenoma-like structures T C II cells, macular cells and modified muscle cells, they become endocrine-like and foamy, lying on capillaries, which is a structure of hypernephroma

We recently studied what we think is an interesting tumor, from various view points It gives valuable information on the potentialities of renal tissue and the various ways these potentialities may become appearent

A clinical diagnosis of WILMS tumor was made in a young boy The left renal region was submitted to X-Ray therapy to reduce the size of the tumor Operation was postponed because of pulmonary infection, but after a while it was felt that a nephrectomy should be performed notwithstanding residual pulmonary disease because the tumor was increasing in size A left kidney was thus removed with a tumor like a goose-egg in its inferior pole

The microscopical findings appeared unusual and a thorough study of the specimen was made, with various histological techniques on several hundreds of sections

A basic feature was the presence of a very young blastema of sarcomatous appearance This blastema may be completely undifferentiated and give rise to a highly malignant sarcoma, with many atypical cell divisions, it is also linked by every intermediate stage to more differentiated areas of various types fibrosarcoma, myxosarcoma, leio- and rhabdo-myosarcoma, it shows areas of cartilaginous differentiation and even suggests the evolution into osteosarcoma

It forms embryonic renal tubules, typical of WILMS-tumor Although we studied several such tumors in order to find neurogenesis, the present case is the first one in which we discovered an important nervous proliferation related to tubular formation The appearance of neuroblasts in the tumor fulfills the requirements recalled in a previous chapter on technique (see p 2) the neuro fibrils are stained red by MASSON's trichromic stain whereas the connective fibers stain blue with anilin blue, they are yellow after VAN GIESON's staining when collagen fibers are red, they are impregnated by ROGERS' silver technique and remain unaffected by FOOT's silver impregnation of reticulin Their morphology is similar to their structure in typical nervous system Such neuroblasts differentiate from a common blastema giving rise to tubular sketches to which they are linked by many transitional stages

The tumor itself arises from the kidney in which neoplastic degeneration is seen It is not our purpose here to deal at full length with other particulars of this tumor, such as the relationship between various parts of the normal nephron and neoplastic disease The presence of hypernephroid tissue related to the above mentioned structures is of great interest for the discussion to follow

Interpretation of these facts is insecure if one does not admit that the renal blastema contains neurogenic elements The existence of a lumbar ectomesenchyme arising form the neural crest and contributing to the formation of the renal blastema is the logical way to explain this [1] So far we are in complete agreement with the facts described by MASSON (1938, [132]) MASSON thus recalled the existence of nervous elements in certain embryonal adenosarcomas of the kidney and showed that the neuroblasts were closely linked to the embryonal renal cells, this led him to admit the contribution of the neural crest to the renal blastema The ectomesenchyme is capable of producing a great many tissues such as connective tissue, cartilage and muscle, as usual mesodermic mesenchyme does

Hypernephroid tissue being present in a tumor with neurogenesis and being morphologically related to it, we wondered whether the ectomesenchyme would not afford a solution to the problem of the hypernephroma In other words, would not the ectomesenchymatous origin of renal hypernephroma clarify this whole field of research?

It should be noted here that PICK (1927, [133]) described an unusual renal tumor, a peripheral hypernephroid growth surrounding a gangliocytoma In his opinion, this was a combined neoplasm, a typical hypernephroma arising from a "Struma aberrans suprarenalis renis" (GRAWITZ, 1883, [84]), from both elements of the ectopic suprarenal rest, "Nebennebennierchen", the cortex

[1] Unless one admits that there is no specificity in the production of nervous tissue (see the historical survey of the development of the sympathetic nervous system by VAN CAMPENHOUT 1930 [190])

and the medulla For him this was a capital sign in favor of GRAWITZ' theory, because neither chromaffin tissue, neither sympathetic ganglia are present in the kidneys "Da in der Niere weder chromaffines Gewebe noch sympatische Ganglien vorkommen, bleibe dann als wahrscheinlichster, man kann wohl sagen, einzig moglicher Schluss nur der auf die hypernephrogene Natur der

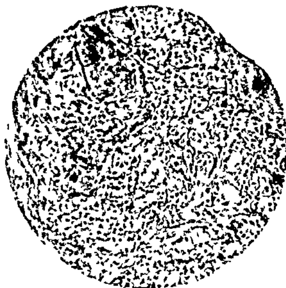


FIG 44 Human semi lunar ganglion showing a nest of para ganglionic cells in the midst of typical nerve cells (compare with the tumor in PICK's case referred to in the text) MASSON's trichrome

gesamten Blastombildung und damit im besonderen also auf die hypernephrogene Natur der hypernephroiden Geschwulstanteile"

We know that nerve cells may exist in the kidneys although they are scarce, we have indications of the existence of paraganglionic cells in close relationship to renal tissue The gangliocytoma in PICK's tumor may thus be from renal origin, and the hypernephroid growth may be of the same origin too But we do not even need the existence of true nervous and paraganglionic cells in a given normal kidney to explain the local origin of such growth The renal adenosarcoma produces sketchy nephrons and sympathogonic capsules The tumor described by PICK may well be a true renal tumor arising from one mesectodermic blastema giving rise to ganglionic cells and hypernephroid tissue as in our above mentioned case In PICK's case the ganglion cells are seen budding in the hypernephroid tissue and the two get very intimately fused We

publish again a photomicrograph of paraganglionic tissue enclosed in a sympathetic ganglion (a state of affairs which is not too unfrequent), the neurectodermic origin of both elements is fairly evident from the embryological viewpoint The similarity between this picture and the one published by PICK is striking If we believe that some hypernephroid tumors associated with neurogenesis are produced by a same blastema, potentialy nervous and nephrogenous, we are able to explain a great many observations, as we pointed out a few years ago

This hypothesis is supported by early embryonic studies showing a mesenchymatous transformation of the peripheral cells of the lumbar ganglionic crest in the presumptive renal area Histogenesis and histology of the kidney show the existence of a juxtaglomerular complex where modified muscle cells and modified tubular cells are in close relationship to nerves The modified muscle cells get the structure of endocrine, paraganglionic cells and this assumption is borne out very clearly by observations of comparative anatomy (epithelioneural complexes) The modified tubular cells assume the appearance of a neuro-epithelium of a sensory type Neurogenesis in renal tumors is another expression of the "neurility" of the renal blastema

When the renal blastema undergoes neoplastic degeneration its possibilities are manifold it may produce more or less typical renal structures, renal cell carcinomas with or without tubule or gland formation, it may also produce various neural crest derivatives, connective tissue, cartilage, bone, muscle sympathoblasts and their derivatives and neuro endocrine cells (see p 12) Such a view would unify the problem of renal tumors, including the ever varying aspects of "hypernephromata" from renal-like structures to endocrine structures [1] The fact that these endocrine structures may mimic adrenocortical morphology is not a difficulty as there are reasons to believe that parts of the cortex of the suprarenal may arise from an ectomesenchyme as happens with the kidney

This leads us to consider another aspect of the same problem

If the "neurility" of the renal blastema is supported by the neural crest derivatives, is the neurectodermic contribution to the lumbar mesenchyme (ectomesenchyme or neurectoderm) exclusive to the kidney and renal area or does it show up somewhere else? The renal area proper is but a section of the urogenital fold which should be investigated thouroughly If in the course of our investigations we find that the renal area is but a part of the whole field where neurectoblastic material forms ectomesenchyme and endocrine cells, our hypothesis would gain strong support

[1] The word H... neph... nign Hyper e aden ma nephroma that there

Neurility is present in the gonads. As Van Campenhout points out in a recent view of the subject (1949, [198]), the testes have the usual nerve supply and epithelioneural bodies. These are of interest. Berger (1923, [13]) was the first one to recognize the interstitial nature of what he called "sympathicotropic" cells, these being true Leydig-cells. It is not our purpose to discuss the whole problem of the sympathicotropic cells, let it suffice to recall their existence in the testicle, in the ovary, and in the vicinity of the gonads of various mammals, their close resemblance to paraganglionic cells although they lack chromaffinity and argentaffinity (Van Campenhout), the fact that they seem to be born on the spot mixed up with nerve fibers or to invade nervous bundles later on. Where do these special cells exactly come from? The apparently conflicting opinions of De Winiwarter (1910, [47]) and Berger (1945, [6]) seem to support the observations made by Van Campenhout. this author (1947, [96]) demonstrated in a series of human embryos the presence of argentaffine cells in the nerves and ganglia near the testicle and the ovary up to the 10 cm. stage, from this stage on, up to the 19 cm. stage for the ovary, and 22 cm. stage for the testis, the nerves do not show anything but fibers and Schwann as well as endoneural cells. Later on cells make their appearance inside the hilar nerves and become similar to the interstitial cells proper of the testis and the ovary. such cells may well develop from the nerve sheath, the cells born in the gland itself (De Winiwarter & Sainmont, 1909, for the ovary) arise from young mesenchyme cells of the stroma much in the same way as the epithelioid cells of the primary arterial wall make their appearance in the kidney.

In a study of the testis in infancy and childhood, Gruenwald (1946, [89]) remarked, when many interstitial cells disappeared shortly after birth, the presence of cell forms which may be stages by which they are transformed into connective tissue cells.

As it seems to happen with the kidney, do neoplastic processes tell us anything about the nature of these cells? The whole subject of tumors in testes and ovaries is terribly confusing. The Leydig-cell tumors are not usually difficult to recognize, typical malignant tumors are very scarce (Masson, 1943, [13]), typical benign tumors are more frequent. It appears from a review of the literature that some Leydig-cell tumors were labelled hypernephroma. As a matter of fact corticosurrenal rests or nests may be found in the vicinity of the gonads (Schiller, 1942, [69], O'Crowley & Rush, 1943, [150], Harvey, 1947, [95], Van Campenhout, 1947, [96] etc.). On the other hand Leydig-cells may be found elsewhere than in the normally located testes and ovaries (Nieberle, 1934, [illegible], Nelson, 1938, [140] and so forth). This led Innes (1942, [105]) to the following conclusions, discussing neoplastic diseases of the testis in animals. As is the case of true tumours of man, the cells of the benign tumour of the calf included in the present series show such a striking resemblance to

normal interstitial cells that their origin seems fairly certain. The concept that this type of tumour is "hypernephromatoid" in nature is unnecessary. The tumour
cells of t
that ad
responsible for the idea of the existence of an hypernephroma testis. It might therefore be suggested that the so called adrenal *rests of the testis are in fact* interstitial cells deposits. Indeed the whole idea of an hypernephroma testis rests on a very insecure foundation.

For us the discussion would be useless if we admitted that the argentaffin— and chromaffin cells, SCHWANN-cells, sympathicotropic cells—and some at *least of the LEYDIG-cells and adrenocortical rests*, represent *only* various aspects of a same fundamental material, the neurectoderm giving rise to an ectomesenchyme.

The coexistence in the testis of a newborn of intranervous sympathicotropic cells and a nest of pheochromic cells (BERGER, 1935,[15]) is readily explained by the same hypothesis.

VAN CAMPENHOUT and WITSCHI state in 1948 ([197]) "... Adrenocortical, *interstitial and thecal cells are closely related, embryologically and cytologically*." This confirmed partly the view expressed by BERGER (1945,[16]) 'We therefore, concur on this point with von WINIWARTER, that the interstitial cells from the sixth month on become almost exclusively located in the theca interna of the deep atretic follicles."

Can the link between adrenocortical rests and sympathicotropic cells be *their common origin from ectomesenchyme if the cortex of the suprarenal is of* mesodermic origin?

Recently, VELICAN (1950,[203]) verified on a series of human embryos, foetuses, newborn and adults the ontogenic evolution of the cortex of the suprarenal. He described a first plasmodial stage beginning after the 26th day (5 to 6 mm. embryo) and extending throughout the whole embryonic life. coelomic epithelium starts budding along the mesenteric root and the cells insinuate between the aorta and mesonephros (Group I). The 7,5 mm. embryo shows coelomic budding on the inner aspect of mesonephros (sexual germinative zone) (Groupe II), one portion of these cells contributes to the constitution of the gonads, another portion reaches the space between the aorta and mesonephros and forms the first "anlage" of the cortex of the suprarenal. *These cells form a coat to a vascular expansion in the same way* as epithelioid cells coat the primary vessel pinched in BOWMAN's capsule. Around this portion the Group I cells form a second "anlage" (the adult cortex), the central zone (called androgenic zone by the author) is a temporary one, its involution begins after birth and its place is finally taken by the concentration

of chromaffin cells in the inner part of the suprarenal (the medullary).

A thorough study of embryology (GRUENWALD 194?, [8]) shows a stage of anonymous mesenchyme between the coelomic proliferation of cords and the final differentiation of the cortex. This may be the stage when ectomesenchymatous elements get mixed up with the purely mesodermic anlage as would happen with gonads.

The bulk of information we have seems to make our hypothesis worth investigating thoroughly. It may clarify greatly not only the embryology, histology and pathology of the lumbar area but also many problems of function. It is an extended and more comprehensive version of the conclusion expressed by APITZ (1943) after a comparative study of renal and suprarenal tumors: Die Gemeinsamkeiten beider Geschwulstformen werden am besten verstandlich wenn mann eine gemeinsame Abstammung von Mesothel als Bildungsmaterial des Nierenblastems und der Nebennierenrinden anlage annimt. He reached this conclusion after finally remarking the unduly high frequency of GRAWITZ tumors in LINDAU's disease and tuberous sclerosis: the bulk of his evidence pointed to a dysontogenic origin of GRAWITZ tumors but not due to embryonic inclusions in the sense of COHNHEIM.

CHAPTER V

Significance of the nervous constituent of the kidney

THUSFAR we have mostly described morphological findings concerning the intrarenal neurogenic elements We shall try to elucidate their possible significance by comparing them to data provided by physiology and experimental pathology Summing up the various observations we are impressed by the special significance of the juxtaglomerular apparatus Our first conclusion however is that the kidney is closely linked to nervous elements it has a definite characteristic of "neurility"

Such "neurility" is shown all over the organ by the extensive nerve supply to the vessels without which vessels the nephron is meaningless, in the kidney the vessels have particular importance because of the excretory function proper to this organ On the background of generalized "neurility" two localized structures stand out 1 the intravenous nerve endings, 2 the juxtaglomerular apparatus As intravenous nerve endings seem to disappear after birth, and as the juxtaglomerular apparatus seems to acquire its extreme differentiation after birth, one wonders if these two structures are not complementary elements of a regulatory mechanism The analysis of each structure

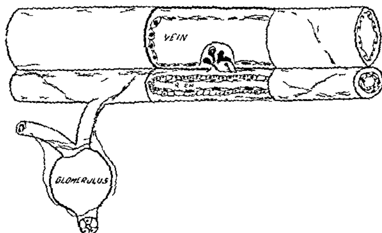
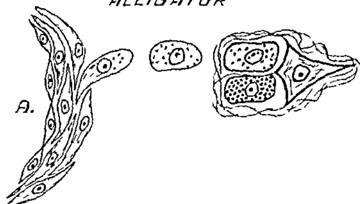


FIG 45 Semi diagrammatic drawing to emphasize the relationship between the intravenous nerve endings, the perivascular plexus and a glomerulus Newborn mouse Silver impregnation

seems to support this hypothesis In a previous discussion of the possible meaning of intravenous nerve endings, we reached the conclusion that they

could not be anything but sensory organs reacting to the modifications of the blood flow and the chemical changes in the blood They would initiate reflex actions regulating the blood supply to the nephron, the effectors being the muscles of the vascular walls The analysis of the juxtaglomerular apparatus is more difficult If we first confine ourselves to the macula densa, we may point



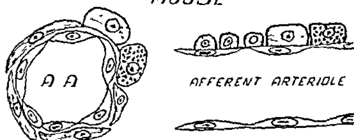


Fig. 46 A diagrammatic comparison between the changes occuring in the myocytes of the arterial media in the hilum of the kidney of the alligator and along the afferent arteriole of the mouse

out that it is a nearly constant feature in the periphery of the cortex. it is always located in the same place in the wall of the T.C II, affixed to the vascular pole of the glomerulus It is in very close connection with the urine (diverticula of the lumen) and the underlying structures (opening up of the basal reticular meshwork), for all we know it is quite similar to a sensory epithelium and the nerves running along its basis supply the wall of the glomerular arterioles It

seems thus probable that it initiates short reflex actions by influencing the arteriolar walls, acting more or less like the intravenous nerve endings found at the earlier stages This possibility is emphasized by the definite local modifications of the arteriolar walls suggesting a special function of the modified muscle cells (*epithelioid cells and micromuscular sphincter*) The epithelioid cells have an endocrine appearance, previous investigations (alligator) suggest that they belong to the neuro-endocrine group, they thus provide a mechanism for changes in the glomerular vascular bed Such changes as vascular constriction of long duration may lead to nephrosclerosis

Before reaching a nephrosclerotic stage, the kidney adapts its function to the needs of the whole organism It reacts to humoral and nervous stimuli or both, and its reaction is immediate We do not intend to review the renal physiology and physiopathology from the viewpoint of the nerve supply to the kidney We shall briefly mention HAMBURGER's monograph (1936,[91]) on "Physiology of *renal innervation*" *A review of the literature, and personal experimental* researches, lead this author to deny the existence of any secretory nerves the various reactions to interference with the nervous system are readily understood by purely vasomotor changes, some of these vasomotor changes, though, appear difficult to explain, such as difference in behavior of renal arteries on one hand, and arterioles and capillaries on the other hand, certain cases of anuria or oliguria, uremia, and high blood pressure, which are less mysterious to day The influence of the nervous system on renal pathology, which is secundary in HAMBURGER's study, is the main subject of the monograph by REILLY and co-workers (1942, [64]), these authors succeeded in reproducing *a large field of human pathology by their experiments of acute and chronic* irritation of the renal nerves, they induced chronic glomerulo-nephritis with hematuria, uremia and high blood pressure leading to final nephrosclerosis TRUETA and co-workers (1947, [187]) made a refined study of renal circulation which taught us the mechanism of the medullary shunt of renal blood and the direct bearing of nervous action on this shunt by way of the splanchnic nerves VAN GELDEREN (1949, [202]) studied the physiology of kidney innervation on patients submitted to splanchnicectomy or *enervation of the kidney He* does not present a conclusive evidence of the existence of proper tubular nerves

The extended conception of a neurogenic contribution to the kidney fits well in the picture and the notion of a juxtaglomerular regulating mechanism proves useful The way the glomerulus shuts off or opens may explain clinical pathology, a good example of this is the problem of renal hypertension The bearing of this reaction on the onset of high *blood pressure is open to discussion* We must consider a few points

1 The juxtaglomerular complex is usually more developed in the peripheral part of the *renal cortex, than in its* deep layers

2 TRUETA and his co workers have shown that by a reflex action, ischemia of the outer layers of the renal cortex may be produced The reflex vasoconstriction seems thus more severe where the juxtaglomerular complexes are more developed, which is in keeping with the view that these structures are reflex centers regulating the circulation through the glomeruli

3 TRUETA's experiments where made in an attempt to reproduce the "crush syndrome' in which there is anuria and high blood pressure

4 Ischemia of the kidney produces high blood pressure [GOLDBLATT & ali (1934, 73 & sq)]

Thus reflex ischemia of the renal cortex may well be the cause of high blood

be of endocrine origin (experiments with transplanted kidneys, isolation of renin, angiotonin, etc)

The question immediately arises where does the hypertensive hormone come from? We have no definite answer to this question yet Two possibilities are open

1 The epithelioid cells of the arteriolar media (GOORMAGHTIGH),

2 Epithelial cells from the nephron, either in the normal nephron, or in the so called BECHER , FEYRTER , PETER cells (free islets cells)

Morphological studies show no fundamental difference between the islet cells and some normal tubular cells Modified muscle cells and tubuloid cells have both been supposed to secrete an hormone modifying the tonus of the vascular walls Whichever of these cells are endocrine, one supposes that under conditions of abnormal stimulation they secrete an excess of vasoconstricting hormone, thus producing a generalized high blood pressure *(in the acute phase)*

Moreover are the tubular cells and epithelioid cells so different?

1 The muscular coat of the glomerular arterioles arises from the loose mesenchyme from which the S shaped tubular sketch also differentiates This *mesenchymatous appearance, of course, may be a known mask put on different cells*

2 The early muscular coat is epithelioid

3 It may become granular and secretory like

4 Smooth muscle cells of the media may bud and produce paraganglionic like structures which are closely related to nerves in epithelioneural bodies On the other hand we know the neurogenic potentiality of the nephronic anlage

After all the tubular cells of the macular segment and the epithelioid cells of the juxtaglomerular arteriole may both arise from an ectomesenchyme, and both secrete one or several hormones regulating the blood flow through the

glomeruli An exhaustive discussion of this subject would lead us much too far, and is beyond the scope of our work

The endocrine secretion does not explain the renal hypertension of long standing, although it explains the acute one, such as in eclampsia or nephritis (scarlet fever, etc) *The removal of ischemic kidneys after a certain lapse of* time does not cure hypertension, the mechanism of which seems different Knowing the extensive innervation of the blood vessels of the kidney, we wondered if these vascular walls were not sensitive areas, like the carotid sinus and aortic areas regulating the blood pressure In the cardio-aortic and carotidal zones, a local decrease in blood pressure, initiates a reflex by which the inhibition of the centers in the brain stem is lessened and the systemic blood pressure elevated The reverse is also true, a local increase in blood pressure in the cardio-aortic and carotidal zones, stimulates the depressor nerves, increases the inhibition of the centers, and decreases the systemic blood pressure The complete section of the depressor nerves produces a permanent high blood pressure In the kidney, the narrowing of the renal artery decreases the blood pressure in the renal vascular bed and is followed by high blood pressure We do not know the effect of increasing the blood pressure in the renal vascular bed On the other hand, we know that in parabiotic twin rats, a bilateral nephrectomy in one of the twins produces a high blood pressure in that twin exclusively, this postulates a non humoral mechanism and a purely nervous action

"The effect of denervation of the kidneys on systemic blood pressure seems to amount to nothing"

"High blood pressure may be produced by narrowing the renal artery of a denervated or transplanted kidney"

These two propositions seem to ruin the comparison between the depressor *areas and the renal area The second proposition*, as a matter of fact, does not exclude the existence of renal depressor nerves, the existence of an endocrine activity is demonstrated now, and if two mechanisms exist, it seems that the endocrine one is working in this case, the nerves being disconnected So we are *left with the first objection* Let us assume for the sake of argument that we have renal pressosensitive areas, working in the same way as the cardio aortic and carotidal zones What would one expect from a complete denervation of both kidneys? No depressor impulses will reach the centers from the renal areas and the blood pressure should be elevated But, at the same time, if still powerful impulses arise from the juxta-cardiac zones the vasomotor centers are maintained at a low level of action The problem is thus a question of deciding which are the most powerful impulses If the cardio-aortic and sino carotidal ones are the most powerful, the negative result of denervation of the kidney is well explained, but if this is the case how can one explain the *hypertensive effect of*

prolonged ischemia of the kidney Two points must be taken into view
1 ischemia produces first endocrine hypertension, and the hormone may also modify the reactivity of the centers, which may become regulated to high
2 ischemia, and low intrarenal blood pressure, produces a continuous decrease of the inhibitor impulses from the kidney, thus slowly upsetting the

is established, the kidneys may be removed without relieving the disease of the central vasomotor areas The experiment on parabiotic twins excludes an hormonal factor and postulates the existence in the kidney of some sort of a sensory zone producing depressor effects the onset of high blood pressure makes one wonder what the activity of the juxta cardiac depressor nerves may be in this case, the only possible answer being that they are overwhelmed by the pressor demand arising from the renal area

HEYMANS and BOUCKAERT (1939 [6]) studied experimental high blood pressure from both viewpoints of renal ischemia and exclusion of cardio aortic and sino carotidal nerves Their very interesting results may be summarized as follows

1 Section of cardio aortic and sino carotidal nerves which by reflex tonus action keep the blood pressure at a moderate level, initiates a severe hypertension of long duration by a neurogenic, sympathetic mechanism

2 The kidney is apt to secrete in the circulating blood a vasoconstrictive substance which *at the same time, lessens the tonus* of the nerves depressing the blood pressure it thus produces a high blood pressure

3 A By total sympathectomy (except of the kidneys and suprarenals) the not disconnected sympathetic is hyperstimulated but does not produce high blood pressure

B Section of cardio aortic and sino carotidal nerves in this case lets loose progressive hypertension of long duration although it is completely uneffective in totally sympathectomized dogs

C Renal sympathectomy exclusively reduces blood pressure to normal levels

We are thus faced with a high blood pressure of an exclusively neurogenic and renal origin (vasospastic) although it is necessarily humoral in its peripheral mechanism after an extensive sympathectomy In relation to the previous discussion it is interesting to note that the depressor nerves as such (carotidal and cardio aortic) may become hypotonic under the influence of renal ischemia renal ischemia thus activates hypertensive reflexes (BOUCKAERT, FLAUT & HEYMANS 1937)

To sum up the function of the juxtaglomerular apparatus, on
The modified muscle cells have an endocrine appearance and ar
the suprarenal like cells found in the hilum of the kidney They m
vascular hormone for the glomerular tuft, an hypersecretion of this
followed by the flooding of the general circulation by it, followed b
striction and hypertension The secretion of this hormone may be r
various ways some characteristics of the blood flowing through the
be adequate stimuli the nerves of the arteriolar wall may influenc
fied cells reacting to stimuli arising in the kidney itself (short reflex
macular area, for instance) or outside the kidney (long reflexes fo
splanchnic nerves) The endocrine substance would act on the mic
cells and other contractile cells present in their vicinity A prolo
constriction will bring the degeneration of the glomerular tuft and
the glomerular vessel as such It should be emphasized that in a nor
oning kidney the role of the macula densa is very important adapt
culation through the nephron to the composition of urine (this
either by a nervous or by an endocrine mechanism)

As we said previously the hypertension may also be the result of
of other vasosensitive zones but in the long run when nephrectom
relieve the high blood pressure any more the disease is probab
localized to the brain stem and mechanically incurable

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